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The translational controlled tumour protein TCTP: Biological functions and regulation

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Abstract
The Translational Controlled Tumour Protein TCTP (gene symbol TPT1, also called P21, P23, Q23, fortilin or histamine-releasing factor, HRF) is a highly conserved protein present in essentially all eukaryotic organisms and involved in many fundamental cell biological and disease processes. It was first discovered about 35 years ago, and it took an extended period of time for its multiple functions to be revealed, and even today we do not yet fully understand all the details. Having witnessed most of this history, in this chapter, I give a brief overview and review the current knowledge on the structure, biological functions, disease involvements and cellular regulation of this protein. TCTP is able to interact with a large number of other proteins and is therefore involved in many core cell biological processes, predominantly in the response to cellular stresses, such as oxidative stress, heat shock, genotoxic stress, imbalance of ion metabolism as well as other conditions. Mechanistically, TCTP acts as an anti-apoptotic protein, and it is involved in DNA-damage repair and in cellular autophagy. Thus, broadly speaking, TCTP can be considered a cytoprotective protein. In addition, TCTP facilitates cell division through stabilising the mitotic spindle and cell growth through modulating growth signalling pathways and through its interaction with the proteosynthetic machinery of the cell. Due to its activities, both as an anti-apoptotic protein and in promoting cell growth and division, TCTP is also essential in the early development of both animals and plants. Apart from its involvement in various biological processes at the cellular level, TCTP can also act as an extracellular protein and as such has been involved in modulating whole-body defence processes, namely in the mammalian immune system. Extracellular TCTP, typically in its dimerised form, is able to induce the release of cytokines and other signalling molecules from various types of immune cells. There are also several examples, where TCTP was shown to be involved in antiviral/antibacterial defence in lower animals. In plants, the protein appears to have a protective effect against phytotoxic stresses, such as flooding, draught, too high or low temperature, salt stress or exposure to heavy metals. The finding for the latter stress condition is corroborated by earlier reports that TCTP levels are considerably up-regulated upon exposure of earthworms to high levels of heavy metals. Given the involvement of TCTP in many biological processes aimed at maintaining cellular or whole-body homeostasis, it is not surprising that dysregulation of TCTP levels may promote a range of disease processes, foremost cancer. Indeed a large body of evidence now supports a role of TCTP in at least the most predominant types of human cancers. Typically, this can be ascribed to both the anti-apoptotic activity of the protein and to its function in promoting cell growth and division. However, TCTP also appears to be involved in the later stages of cancer progression, such as invasion and metastasis. Hence, high TCTP levels in tumour tissues are often associated with a poor patient outcome. Due to its multiple roles in cancer progression, TCTP has been proposed as a potential target for the development of new anti-cancer strategies in recent pilot studies. Apart from its role in cancer, TCTP dysregulation has been reported to contribute to certain processes in the development of diabetes, as well as in diseases associated with the cardiovascular system. Since cellular TCTP levels are highly regulated, e.g. in response to cell stress or to growth signalling, and because deregulation of this protein contributes to many disease processes, a detailed understanding of regulatory processes that impinge on TCTP levels is required. The last section of this chapter summarises our current knowledge on the mechanisms that may be involved in the regulation of TCT

Keywords
biological, protein, tctp:, functions, regulation, tumour, controlled, translational

Chapter 4
The Translational Controlled Tumour Protein TCTP: Biological Functions and Regulation

Ulrich-Axel Bommer

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Apart from its involvement in various biological processes at the cellular level, TCTP can also act as an extracellular protein and as such has been involved in modulating whole-body defence processes, namely in the mammalian immune system. Extracellular TCTP, typically in its dimerised form, is able to induce the release of cytokines and other signalling molecules from various types of immune cells. There are also several examples, where TCTP was shown to be involved in antiviral/antibacterial defence in lower animals. In plants, the protein appears to

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have a protective effect against phytotoxic stresses, such as flooding, draught, too high or low temperature, salt stress or exposure to heavy metals. The finding for the latter stress condition is corroborated by earlier reports that TCTP levels are considerably up-regulated upon exposure of earthworms to high levels of heavy metals.

Given the involvement of TCTP in many biological processes aimed at maintaining cellular or whole-body homeostasis, it is not surprising that dysregulation of TCTP levels may promote a range of disease processes, foremost cancer. Indeed a large body of evidence now supports a role of TCTP in at least the most predominant types of human cancers. Typically, this can be ascribed to both the anti-apoptotic activity of the protein and to its function in promoting cell growth and division. However, TCTP also appears to be involved in the later stages of cancer progression, such as invasion and metastasis. Hence, high TCTP levels in tumour tissues are often associated with a poor patient outcome. Due to its multiple roles in cancer progression, TCTP has been proposed as a potential target for the development of new anti-cancer strategies in recent pilot studies. Apart from its role in cancer, TCTP dysregulation has been reported to contribute to certain processes in the development of diabetes, as well as in diseases associated with the cardiovascular system.

Since cellular TCTP levels are highly regulated, e.g. in response to cell stress or to growth signalling, and because deregulation of this protein contributes to many disease processes, a detailed understanding of regulatory processes that impinge on TCTP levels is required. The last section of this chapter summarises our current knowledge on the mechanisms that may be involved in the regulation of TCTP levels. Essentially, expression of the TPT1 gene is regulated at both the transcriptional and the translational level, the latter being particularly advantageous when a rapid adjustment of cellular TCTP levels is required, for example in cell stress responses. Other regulatory mechanisms, such as protein stability regulation, may also contribute to the regulation of overall TCTP levels.

4.1 Introduction

Despite there being more than 300 scientific publications on ‘TCTP’ that have been published on this protein over a period of 35 years, it is still difficult to give a brief, comprehensive statement on its functional importance. Typically, papers on this protein start with a sentence such as: ‘TCTP is a highly-conserved, multifunctional protein involved in important biological and disease processes.’ This reflects the fact that by now, many functional aspects of this protein have been revealed, many of which are highly relevant to core biological and medical problems. The recent increasing interest in this protein is also reflected by the fact that 15 review articles on TCTP have already been published, all but two (Bommer and Thiele 2004; Telerman and Amson 2009) within the last 5 years. However, most of these articles focus on specific aspects of the TCTP literature, and they are spread over a wide

range of journals. I feel therefore it is a very worthwhile undertaking by Amson and Telerman to assemble this new collection of up-to-date reviews into one single book. It should be a useful guide for the still growing 'TCTP community', which currently comprises research groups from about 25 countries.

4.1.1 The 'Translationally Controlled Tumour Protein TCTP': Names and History

The 'TCTP story' had a humble beginning with less than ten papers published during the 1980s by three research groups, all interested in protein synthesis and in the hunt for translationally controlled proteins. Initially, the protein was termed according to its approximate molecular mass as Q23 (G. Thomas, Basel; Thomas et al. 1981), P21 (G. Brawermann, Boston; Yenofsky et al. 1982) or as P23 (H. Bielka, Berlin-Buch; Bohm et al. 1989). At this time, the function of the protein was completely unknown, and its most distinguished property was the ability to be rapidly up-regulated upon growth induction of serum-starved murine cells, in a manner insensitive to inhibition by actinomycin D (Thomas et al. 1981; Bohm et al. 1989). Even the publication of the first cDNA sequences of mouse P21 (Chitpatima et al. 1988) and of its human homologue (Gross et al. 1989) did not shed any light on its possible function, as the derived amino acid sequence did not display similarity to any other known protein sequence, and since then, the protein is listed in the databases as a separate 'family'. It was in the latter publication (Gross et al. 1989) that the name 'translationally controlled tumour protein' was coined, since the cDNA sequence had been derived from a human mammary carcinoma.

The first report on a functional association of TCTP appeared in 1995. Susan MacDonald and co-workers (Baltimore) identified an extracellular function of this protein as 'histamine-releasing factor' (HRF) present in biological fluids of allergic patients (MacDonald et al. 1995). This discovery led to a series of studies exploring the extracellular signalling function of HRF/TCTP in allergic and inflammatory responses, as recently reviewed by Dr. MacDonald (2012a, b).

The first studies on intracellular functions of TCTP reported its Ca^{2+}-binding activity (Haghighat and Ruben 1992) and its microtubule association. Our study revealed that TCTP/P23 is bound to microtubules, inclusive of the mitotic spindle, in a cell-cycle-dependent manner, and that it has microtubule-stabilising activity (Gachet et al. 1999). Subsequently, a whole array of additional interaction partners of TCTP/HRF have been identified (reviewed in Kawakami et al. 2012; Bommer 2012; Acunzo et al. 2014).

Another milestone in the unravelling of TCTP's function was the demonstration of its anti-apoptotic activity by Ken Fujise's group (Houston) (Li et al. 2001), exactly 20 years after its initial discovery (Thomas et al. 1981; Yenofsky et al. 1982). Based on their findings, these authors invented the name 'fortilin' for this protein. Their discovery led to a large number of additional studies on the cytoprotective role of

TCTP/fortilin, which showed that the protein is rapidly up- (or down-)regulated in response to a wide array of cellular stresses and that it is involved in a range of cellular defence pathways (reviewed in Bommer 2012; Acunzo et al. 2014).

Despite its name, a convincing demonstration that TCTP is implicated in cancer came only relatively late. Instrumental in this was the experimental 'tumour reversion model' developed by the Telerman group (Telerman and Amson 2009; Tuynder et al. 2002, 2004). Naturally, the cancer aspect of TCTP's 'function' has recently attracted increasing attention, as documented by the about 40 papers and 6 review articles (Telerman and Amson 2009; Bommer 2012; Acunzo et al. 2014; Amson et al. 2013, 2011; Chan et al. 2012a; Efferth 2006; Koziol and Gurdon 2012) on 'TCTP and cancer' that appeared only within the last 10 years.

Further additions to the complex story of the naming of this protein are in reports on TCTP orthologues in non-vertebrate animals, lower eukaryotes and plants. Typically, in these papers, a two-letter suffix before 'TCTP' indicates the species, from which the protein sequence was derived (see Gutierrez-Galeano et al. (2014) for an example). The yeast orthologue of TCTP was named 'microtubule and mitochondria interacting protein' (Mmi1p) (Rinnerthaler et al. 2006), but in another paper, it was also identified as the 'translation-machinery-associated protein 19' (TMA19) (Fleischer et al. 2006), and yet the gene symbol in yeast is YKL056c. In contrast, the gene symbol in higher eukaryotes is TPT1, for 'tumour protein, translationally controlled-1' (Thiele et al. 2000).

4.1.2 Gene Structure and mRNA

The first structure of a TPT1 gene (for rabbit) was characterised in Bernd Thiele's group in Berlin; the gene was found to comprise about 4000 nucleotides, beginning at the transcription start site, and to consist of 6 exons and 5 introns, where the last exon comprises the entire 3′-UTR of the mRNA (Thiele et al. 1998). A very similar structure was also reported for the mouse (Fiucci et al. 2003) and the human (Andree et al. 2006) TPT1 gene. The latter has been mapped to chromosome 13, q12-->q14 (MacDonald et al. 1999), the mouse gene to chromosome 14 (Fiucci et al. 2003) and the pig TPT1 gene to chromosome 11 (Yubero et al. 2009), in a genomic context that is similar to that of the human chromosomal location.

The promoter regions of the active TPT1 gene were further investigated for the rabbit (Thiele et al. 1998), mouse (Fiucci et al. 2003) and human (Andree et al. 2006) genes. They displayed a large number of transcription factor-binding motifs, i.e. 10–15 motifs within the 450 nucleotides adjacent to the transcription start site. Of these, seven motifs were conserved between all five mammalian species inspected, and the activity of the tandem CREB transcription factor-binding site was experimentally demonstrated for the human TPT1 gene (Andree et al. 2006).

The early characterisation and mapping of the TPT1 gene was complicated by the fact that there is a considerable number of processed or unprocessed pseudogenes in mammalian genomes, which is apparently not the case in lower

eukaryotes, fungi, plants and non-mammalian animals (Hinojosa-Moya et al. 2008). Several of these pseudogenes have been studied in some detail in the rabbit (Thiele et al. 2000) and in mouse (Fiucci et al. 2003), and only few were found to have the potential to produce a protein product.

Northern blot analysis of TCTP mRNAs from a range of different tissues revealed that all cells produce two different TCTP mRNA species in both rabbits (Thiele et al. 2000) and in humans (Andree et al. 2006), the longer one bearing a 320 nucleotide extension at the 3′-end, which is generated by an additional polyadenylation site. These two isoforms comprise a total of about 800 and 1200 nucleotides, respectively (Andree et al. 2006). The ratio between the two mRNA species differs considerably between different tissues, but the short mRNA is always in excess (Thiele et al. 2000). The importance for the production of these two different mRNA species has not yet been elucidated, but interestingly, in mouse tissues, there was only one TCTP mRNA isoform detected (Fiucci et al. 2003).

Mammalian TCTP mRNAs contain an open reading frame of 519 nt (172 amino acids), a 5′-UTR of about 100 nt and a 3′-UTR of about 200 nt or of 520 nt for the longer isoform (Thiele et al. 2000). A particular feature of TCTP mRNAs, indicative for translational regulation, is a 5′-terminal oligopyrimidine tract (5′-TOP): sequence 5′-CTTTTCCG . . . for the human, mouse and rabbit mRNAs (Thiele et al. 1998, 2000; Fiucci et al. 2003). The 5′-TOP motif is a hallmark for a specific group of mRNAs that are under translational control through the mTOR complex 1 (mTORC1) signalling pathway (Meyuhas and Kahan 2015; Yamashita et al. 2008). We have recently demonstrated that growth induction of TCTP expression is indeed regulated through this pathway (Bommer et al. 2015).

A second feature is the high CG-content in the 5′-UTR (about 80% in the mouse sequence), which indicates the potential of the molecule to form a high degree of secondary structure. Our lab has indeed shown that full-length TCTP mRNA of the mouse is a very structured molecule, the structure formation being dependent on the presence of the 5′- and the 3′-UTR. Consequently, the full-length mRNA molecule is poorly translated, in contrast to a truncated version devoid of the 5′- and 3′-UTRs (Bommer et al. 2002). Yet another feature is the presence of several AUUUA elements in the 3’-UTR of the TCTP mRNA (Gross et al. 1989; Thiele et al. 2000). Such elements typically target cytokine mRNAs for destabilisation; however, the AUUUA motifs present in TCTP mRNA do not comprise the complete consensus sequence for such destabilisation elements. To my knowledge, there is currently only limited experimental evidence for regulated degradation of TCTP mRNA. In contrast, the aforementioned high degree of structure formation (Bommer et al. 2002) would indicate that it is a rather stable mRNA molecule, consistent with the early observation that a large proportion of the mRNA exits in untranslated mRNP particles (Yenofsky et al. 1982).

4.1.3 Molecular Structure, Conservation and Interactions

As mentioned above, elucidation of the amino acid sequence of TCTP did not reveal anything about the functional implication of the protein. Only the first publication of the solution structure of TCTP from the fission yeast (Thaw et al. 2001) provided some structure-derived information about a possible functional association of the protein. It revealed similarity to the Mss4/Dss4 family of proteins, a group also called guanine nucleotide-free chaperones.

The amino acid sequences of TCTP are highly conserved throughout all eukaryotic taxa; several sequence comparisons have been published recently (Yubero et al. 2009; Hinojosa-Moya et al. 2008; Thayanithy 2005), and a detailed phylogenetic analysis using 93 different TCTP sequences revealed that, by and large the phylogeny of TCTP sequences is consistent with the evolutionary history, although there were some exceptions (Hinojosa-Moya et al. 2008).

The three-dimensional structures of the following TCTP proteins were solved and are deposited in the databases: The solution structures of fission yeast (Thaw et al. 2001) and human TCTP (Feng et al. 2007a), as well as the crystal structures of *Plasmodium knowlesi* (Vedadi et al. 2007) and human TCTP (Susini et al. 2008) at 2 Å resolution. A mutant version of human TCTP showing a structure very similar to the normal protein (Dong et al. 2009) can be found as well. Figure 4.1 shows the solution structure of human TCTP as an example, since in the crystal structure, the flexible loop domain is not displayed. The figure demonstrates the three major domains of the TCTP protein.

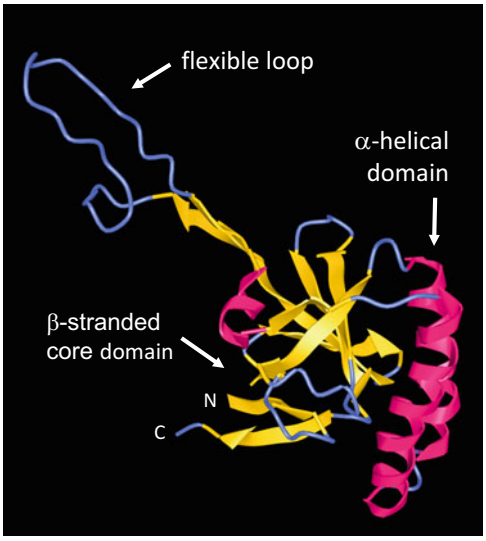

Fig. 4.1 NMR structure of human TCTP. Secondary structure elements are highlighted as follows: *magenta*: α-helices, *yellow*: β-sheets, *blue lines*: unstructured areas; major domains are indicated (from: Feng et al. 2007a, PDB ID: 2HR9)

A considerable number of 3D structures of other members of the TCTP family, in particular from various plant species, have been predicted (Gutierrez-Galeano et al. 2014; Hinojosa-Moya et al. 2008; Berkowitz et al. 2008), based on the experimentally determined 3D-structures of TCTP and on sequence comparisons. Phylogenetic comparisons showed that the predicted tertiary structure of TCTP proteins is in general highly conserved throughout evolution (Gutierrez-Galeano et al. 2014; Hinojosa-Moya et al. 2008), although there are some deviations in the TCTP structure of lower eukaryotes (Hinojosa-Moya et al. 2008) and some species of chlorophyta do not seem to have a TCTP gene at all (Gutierrez-Galeano et al. 2014). In the plant kingdom, two principal types of TCTP structures are being distinguished, with some plants having the gene for one of the two types, whereas other ones have genes for both types (Gutierrez-Galeano et al. 2014).

Since TCTP is involved in a wide range of biological processes, it is not surprising that it undergoes interactions with a large number of partner proteins. The distinct domain structure (Fig. 4.1) is likely to enable the protein to interact with many other proteins (and with itself) in a specific manner. In 2012, Toshi Kawakami published a review article summarising the TCTP/HRF interactions known at the time (Kawakami et al. 2012). In the meantime, a considerable number of additional interaction partners were identified, so it is timely now to compile an updated list, as shown here in Table 4.1. This table provides an overview on the many interaction partners and biological processes TCTP/fortilin/HRF is involved in, some of which will be discussed in the following sections. Recent interaction screens indicate that a much larger number of proteins have the potential to interact with TCTP (see e.g. Li et al. 2016), however only a limited number of those have actually been validated today.

4.2 Biological Functions of TCTP

4.2.1 Maintaining Cell Homoeostasis and Survival

4.2.1.1 Anti-apoptotic Activity: Discovery and Mechanisms

The anti-apoptotic activity of TCTP was originally discovered in Ken Fujise's laboratory, where the name 'fortilin' was coined (Li et al. 2001). Their study described the cytoprotective effect of TCTP/fortilin overexpression against etoposide-induced apoptosis in HeLa cells. Since then, the anti-apoptotic activity of TCTP has been reported on numerous occasions and in a range of different settings, which will be discussed below. Major support for the cytoprotective role of TCTP came from gene-knockout studies in mice, which demonstrated that TCTP-knockout was embryonic lethal, due to excessive apoptosis at an early embryonic state (Susini et al. 2008; Chen et al. 2007a; Koide et al. 2009). The following mechanisms have been proposed to underlie the anti-apoptotic activity of TCTP/fortilin:

Table 4.1 TCTP interaction partners

Biological function	Binding partner	Binding site in TCTP[a]	Biological importance	References
Stress response	Na-K-ATPase	C-terminus	Na-K-ATPase inhibition	Jung et al. (2004), Kim et al. (2008a)
	Sorting nexin 6 (SNX6)		Na-K-ATPase activation	Yoon et al. (2006)
	Ca^{2+}	N- and C- terminus	Ca^{2+}-scavenging	Feng et al. (2007a), Graidist et al. (2007), Kim et al. (2000)
	Vitamin-D3 receptor	α-Helical domain	Ca^{2+}-related processes	Rid et al. (2010)
	Peroxiredoxin-1		Protection from ROS	Chattopadhyay et al. (2016)
	ATM kinase and γH2A.X		DNA damage response (DDR)	Zhang et al. (2012)
	Brahma		Genome stability	Hong and Choi (2016)
	Y-box binding protein 1	N-terminus	Stress response, DNA damage response (DDR)	Li et al. (2016)
	Stress granules		Heat shock protection	Rinnerthaler et al. (2013)
	Ubp3, Cdc48 in yeast		Proteasome inhibition	Rinnerthaler et al. (2013)
	VHL Tumour suppressor		Ubiquitinylation of VHL, stabilisation of HIF-1α	Chen et al. (2013a)
Survival, apoptosis prevention	p53	α-Helical domain	Degradation of p53	Amson et al. (2012), Chen et al. (2011), Rho et al. (2011)
	MDM2/HDM2		Degradation of p53	Amson et al. (2012), Funston et al. (2012)
	Mcl-1	N-terminus	Stabilisation of Mcl-1/TCTP	Liu et al. (2005), Roque et al. (2016), Zhang et al. (2002)
	Bcl-XL	α-Helical domain	T-cell survival	Yang et al. (2005), Thebault et al. (2016)
	Apaf-1		Chemoresistance	Jung et al. (2014)
	Hsp27		Stabilisation of TCTP	Baylot et al. (2012)
	Mitochondria	α-Helical domain	Apoptosis prevention	Rinnerthaler et al. (2006), Susini et al. (2008)

Cytoskeleton, cell cycle/ division	α- and β-tubulin	α-Helical domain		Gachet et al. (1999)
	Microtubules	α-Helical domain	Microtubule stabilisation	Gachet et al. (1999), Jaglarz et al. (2012)
	Mitot./meiotic spindle		Spindle stabilisation	Gachet et al. (1999), Jeon et al. (2016)
	Chfr (checkpoint protein)		Located at spindle	Burgess et al. (2008)
	Actin filaments			Bazile et al. (2009), Tsarova et al. (2011)
	Plk-1 kinase	Flexible loop	Cell cycle progression	Yarm (2002), Cucchi et al. (2010)
	Pim-3 kinase	N-terminus	Stabilisation of Pim-3	Zhang et al. (2013)
	Cdc25C phosphatase		Cdc25C degradation	Chan et al. (2012b)
Early development	ATM kinase		Organ development	Hong and Choi (2013)
	Nucleophosmin		ES cell proliferation	Johansson et al. (2010a)
	Nucleolin		ES cell proliferation	Johansson et al. (2010b)
	Oct-4		ES cell maintenance	Johansson and Simonsson (2010)
	ATG16		Regulation of autophagy	Chen et al. (2014a)
Protein synthesis; growth regulation	eEF1A		Stabilisation of eEF1A-GDP	Cans et al. (2003)
	eEF1Bβ	α-Helical domain and core domain	Inhibition of the GEF activity of eEF1Bβ	Cans et al. (2003), Langdon et al. (2004), Wu et al. (2015)
	40S ribosomal subunit		Ribosome binding in yeast	Fleischer et al. (2006)
	Rheb GTPase	Core domain	Drosophila, TOR activation	Dong et al. (2009), Hsu et al. (2007)
	14-3-3 proteins	(TCTP and Rheb)	Drosophila, organ growth	Le et al. (2016)
Extracellular function and allergic response	TSAP6		TCTP export in exosomes	Amzallag et al. (2004)
	TCTP		Dimerisation	Kim et al. (2009a), Lucas et al. (2014)
	Specific antibodies	TCTP-dimer		Kashiwakura et al. (2012)
	Haemin	His76/His77	TCTP dimerisation	Lucas et al. (2014)

[a]Where determined, the location of the binding site in the respective TCTP domain (Fig. 4.1) is indicated

1. *Cooperation with other anti-apoptotic proteins*. Two anti-apoptotic proteins of the Bcl-2 family have been shown to interact with TCTP, i.e. Mcl-1 (Liu et al. 2005; Zhang et al. 2002) and Bcl-XL (Yang et al. 2005). In the case of Mcl-1, it was reported that TCTP stabilises Mcl-1 (Liu et al. 2005) and vice versa (Zhang et al. 2002), but another study also showed that both proteins are able to exert their anti-apoptotic activity independently of each other (Graidist et al. 2004). Recently, the interaction of TCTP with Bcl-XL was investigated in more detail (Thebault et al. 2016). This study demonstrated that TCTP has a BH3-like domain. Binding to such BH3 domains (Bcl2 homology domain 3) typically inhibits anti-apoptotic proteins; however, TCTP's BH3-like domain actually activates the anti-apoptotic activity of Bcl-XL (Thebault et al. 2016). Thus, in both cases, Mcl-1 and Bcl-XL, interaction with TCTP stimulates or maintains their activity.
2. *Preventing apoptotic mechanisms*. The pro-apoptotic protein Bax promotes the execution of apoptosis by inserting itself via an α-helical domain into the mitochondrial membrane, forming a homo- or heterodimer (with Bak) and inducing membrane permeability and cytochrome c release. A detailed study by the Telerman-group demonstrated that the α-helical domain of TCTP (Fig. 4.1) resembles that domain of Bax, which is crucial for its activity (Susini et al. 2008). They also showed that TCTP, with its α-helical domain, is able to insert itself into the mitochondrial membrane and to prevent the dimerisation and activation of Bax. Translocation of TCTP (Mml1) to the mitochondrial surface was also observed in yeast after mild oxidative stress (Rinnerthaler et al. 2006). Another apoptotic mechanism affected by TCTP is the formation of the apoptosome. A core component of this structure is the apoptotic protease activating factor (Apaf-1), whose inactivation has been implicated in carcinogenesis and the development of anticancer drug resistance (Fadeel et al. 2008). A recent report by the group of Kyunglim Lee documented that TCTP binds to Apaf-1 via its caspase recruitment domain and inhibits the activation of caspase 9 (Jung et al. 2014).
3. *Antagonism to p53*. The tumour suppressor protein p53 is a very powerful pro-apoptotic agent, so interfering with its activity is an essential strategy for anti-apoptotic players. Conversely, down-regulation of anti-apoptotic proteins forms part of the armory of p53 to promote apoptosis. Indeed down-regulation of TCTP through activation of a (temperature-sensitive) mutant protein of p53 (Tuynder et al. 2002; Bommer et al. 2010) was an initial observation in this context. The mutual antagonism between p53 and TCTP was then described by three groups in brief succession (Amson et al. 2012; Chen et al. 2011; Rho et al. 2011). The underlying mechanisms involved in this included the following: (1) TCTP stimulates degradation of p53 (Rho et al. 2011) by binding to P53-MDM2 complexes [or to HDM2 (Funston et al. 2012)] and promoting MDM2-mediated ubiquitination and degradation of P53 (Amson et al. 2012). (2) P53 as a transcription factor binds to a P53 responsive element in the promoter region of the TPT1 gene and inhibits its transcription (Amson et al. 2012) [although p53-dependent *induction* of TPT1 transcription by has also been reported (Chen et al. 2013b)]. (3) TCTP levels are also translationally regulated

through the PI3-kinase/Akt/mTORC1 signalling pathway (Bommer et al. 2015). Since this pathway is targeted by p53, through induction of its negative effectors PTEN and TSC2 (Feng et al. 2007b), this implies that p53 also interferes with TCTP synthesis at the translational level.

4.2.1.2 Involvement in Cellular Stress Responses

The cytoprotective action of TCTP has been demonstrated in a variety of cellular stress responses, such as heat shock, oxidative, genotoxic or Ca^{2+}-stress and in a range of different cell lines. These effects of TCTP also contribute to its involvement in the development of drug resistance, a frequent problem in chemotherapeutic treatment of cancer.

1. *TCTP and heat shock*. Work on TCTP proteins from parasitic organisms (*Trichinella* and Filarials) showed that TCTP behaves as a heat-shock protein with chaperone-like activity. Its synthesis is induced after heat-shock treatment (Gnanasekar et al. 2009; Mak et al. 2007). Both human and filiarial TCTP (from *Schistosoma mansoni*) bind to denatured and native proteins, protecting the latter from thermal denaturation (Gnanasekar et al. 2009). The yeast homologue of TCTP, Mml1, has been shown to associate with stress granules in heat-shocked cells and to modulate proteasome activity (Rinnerthaler et al. 2013).
2. *TCTP in oxidative stress*. Another filarial TCTP protein (from *Brugia malayi*) was reported to display anti-oxidant activity. The reduced form of BmTCTP was able to protect DNA from oxidative damage (Gnanasekar and Ramaswamy 2007). Similarly, TCTP prevented hydrogen peroxide-induced cell death in murine fibroblasts (Nagano-Ito et al. 2009). Lucibello et al. studied the behaviour and role of TCTP in a panel of cancer cell lines under oxidative stress conditions. They observed that TCTP is up-regulated in these cells under mild oxidative stress, whereas strong oxidative stress resulted in reduced TCTP levels and subsequent apoptotic cell death. Increased TCTP levels partially protected cells from oxidation-induced cell death (Lucibello et al. 2011). Similarly, overexpression of TCTP (TMA19) in yeast conferred resistance to arsenite to the cells (Takahashi et al. 2010). A mechanism, by which TCTP (fortilin) could exert this protective effect against ROS-induced cell death, was recently proposed by the Fujise laboratory (Chattopadhyay et al. 2016). They reported that TCTP protects the enzyme peroxiredoxin-1 from degradation and keeps it in an active state by blocking its deactivating phosphorylation by the protein kinase Mst1.
3. *TCTP, genotoxic stress and genome stability*. The participation of TCTP in the sensing and repair of DNA damage was first demonstrated by Zhang and colleagues in 2012 (Zhang et al. 2012). This involved the up-regulation of TCTP after γ-irradiation of cells, its complex formation with the ataxia-telangiectasia mutated (ATM) kinase and with the histone γH2A.X and colocalisation with other DNA-damage marker proteins. Lack of TCTP resulted in severe deficiency in chromosome damage repair. A more recent report on the interaction of

Drosophila TCTP confirmed the (genetic) interaction with the ATM kinase and its activation by TCTP (Hong and Choi 2013). These studies demonstrated the importance of TCTP in maintaining genome stability under genotoxic stress, which is consistent with observations from Fujise's and our own laboratory, showing that TCTP is able to protect cancer cells against the cytotoxicity exerted by DNA-damaging anticancer drugs (Graidist et al. 2004; Bommer et al. 2017). The involvement of TCTP in the development of chemoresistance in cancer chemotherapy has also been emphasised by several other papers (Jung et al. 2014; Takahashi et al. 2010; He et al. 2015; Sinha et al. 2000).

4. *Ca^{2+}-stress and maintenance of ion homeostasis*. Possibly the earliest functional association of the TCTP protein to be discovered was the Ca^{2+}-binding activity of a protein from Trypanosomes (Haghighat and Ruben 1992). Later, it was shown that TCTP levels are regulated in response to perturbations of intracellular Ca^{2+}-homeostasis (Xu et al. 1999). Although TCTP does not have a canonical Ca^{2+}-binding site (Kim et al. 2000), its Ca^{2+}-binding activity has been confirmed by several laboratories using a range of methods (Feng et al. 2007a; Graidist et al. 2007; Kim et al. 2000; Lucas et al. 2014; Arcuri et al. 2004, 2005; Sanchez et al. 1997). However, the different approaches used to map the Ca^{2+}-binding site at the TCTP protein yielded different results (Feng et al. 2007a; Graidist et al. 2007; Kim et al. 2000). Feng et al. demonstrated that it is a weak binding site (Feng et al. 2007a); they provided the NMR structure of human TCTP (Fig. 4.1) and mapped the Ca^{2+}-binding site to a conserved part of the β-stranded core domain, close to the 'hinge' region that connects it to the α-helical domain. This result was consolidated and further refined in a very recent study (Lucas et al. 2014). TCTP/fortilin has been reported to act as Ca^{2+}-scavenger, and this was proposed as a yet another mechanism of its anti-apoptotic activity (Graidist et al. 2007). Indeed, overexpression of TCTP has been shown to protect cells against Ca^{2+}-dependent apoptosis induced by thapsigargin (Graidist et al. 2007; Bommer et al. 2010), a reagent that inhibits the Ca^{2+}-pump of the ER membrane, resulting in a significant increase in cytosolic Ca^{2+}-levels. The notion of TCTP acting as a Ca^{2+}- scavenger, or more generally as a 'buffer-like' molecule for Ca^{2+}, is consistent with its high abundance and with the fact that its binding site is rather weak (Lucas et al. 2014). The importance of such a Ca^{2+}-buffer-like function for TCTP was described for trophoblast cells of the placenta, where it is involved in Ca^{2+}-handling and in its provision for the foetal blood circulation (Arcuri et al. 2005). Similarly, in human prostate epithelial cells, TCTP is the Ca^{2+}-binding protein with the highest expression levels (Arcuri et al. 2004).

Another important player in maintaining intracellular ion homeostasis that is influenced by TCTP is the membrane-bound Na^+,K^+-ATPase. Kyunglim Lee's group discovered that TCTP interacts with the third cytoplasmic domain of the alpha subunit of the Na^+,K^+-ATPase in HeLa cells and inhibits its activity (Jung et al. 2004). They also identified another protein, sorting nexin 6 (SNX6), that binds to TCTP and neutralises TCTP's negative effector activity on the Na^+,K^+-ATPase, but does not have an inhibitory activity towards the enzyme on its own

(Yoon et al. 2006). Since the Na^+,K^+-ATPase has been implicated in the pathogenesis of hypertension, the group went on to employ a transgenic mouse model that overexpresses TCTP. They showed that these mice developed systemic arterial hypertension about 6 weeks after birth, due to reduced Na^+,K^+-ATPase activity and increased intracellular calcium (Kim et al. 2008a).

5. *Other stress conditions*. Regulation of TCTP levels in response to various stress situations in plants has been studied recently. Protection against high or low temperatures, salt stress or flooding are particularly important for plant survival, and TCTP is regulated under all these conditions. For example, a recent study on maize leaves subjected to flooding stress, reported that TCTP was increased in response to flooding stress, possibly mediated by increased production of hydrogen peroxide (Chen et al. 2014b). TCTP from the rubber tree (*Hevea brasiliensis*) was found to be regulated by drought, low temperature, high salt, ethylene, hydrogen peroxide or wounding (Deng et al. 2016; Li et al. 2013). This is consistent with the observation that overexpression of TCTP in *Arabidopsis* resulted in increased drought tolerance of the plants (Kim et al. 2012a). Moreover, in the cabbage (*Brassica oleracea*), TCTP was found to be involved in maintaining tolerance to heat, cold and to salt stresses (Cao et al. 2010). A study on TCTP from cassava (*Manihot esculenta Crantz*) reported that the promoter region of the TCTP gene harbours regulatory elements responsive to sodium chloride and to pathogen infection, and that expression of this gene in bacteria conferred a protective effect against salt stress (Santa Brigida et al. 2014). Two other types of phytotoxic stresses, where TCTP appears to have a protective role, is the stress induced by an excess of aluminium in slightly acidic soil (Ermolayev et al. 2003) and the effect of mercury, as investigated in rice (Wang et al. 2012). These findings relate to one of the earliest observations, which reported an up-regulation of TCTP levels in cellular stresses. This study investigated the effect of heavy metal-contaminated soils from mining areas on earthworms and found that the presence of copper or cadmium in these soils led to an extreme up-regulation of TCTP levels in these animals (Sturzenbaum et al. 1998). Subsequently in mammalian cells, a metal-responsive element was discovered in the TPT1 promoter that is highly responsive to copper (Schmidt et al. 2007), confirming that this regulation occurs largely at the transcriptional level.

4.2.2 Involvement in the Cell Cycle and in Early Development

4.2.2.1 TCTP, a Microtubule Stabilising Protein at the Mitotic and the Meiotic Spindle

The property of TCTP/P23 as a tubulin-binding protein that associates with microtubules in a cell cycle-dependent manner was discovered in our laboratory in the 1990s (Gachet et al. 1999). Using deletion mutations, we characterised the tubulin-

binding domain of TCTP as the part of the molecule, which was later identified as the α-helical domain (Fig. 4.1; Thaw et al. 2001). This domain is characterised by a rather basic charge, compared to the overall very acidic charge of the protein; 58% of all basic amino acids are located in this domain, which also shows similarity to the tubulin-binding domain of the canonical microtubule-associated protein MAP-1B (Gachet et al. 1999). Furthermore, we established that overexpression of TCTP/P23 results in microtubule stabilisation, and we showed that the protein binds to the mitotic spindle, but is detached from the spindle during metaphase-anaphase transition (Gachet et al. 1999). Not shown in this paper are our results on mitotic phosphorylation of TCTP/P23 (Fig. 4.2). In this experiment, we tested the TCTP phosphorylating activity in cell extracts from synchronised HeLa cells at different time points after release from the S-Phase block (Fig. 4.2a). The isoform pattern of TCTP in these cells was analysed by 2D electrophoresis in the lab of Jean-Charles Sanchez, Geneva (Fig. 4.2b). These results demonstrated that TCTP phosphorylating activity is low throughout the cell cycle, but peaks sharply (nearly ten-fold) in mitosis, which is consistent with a brief occurrence of an additional

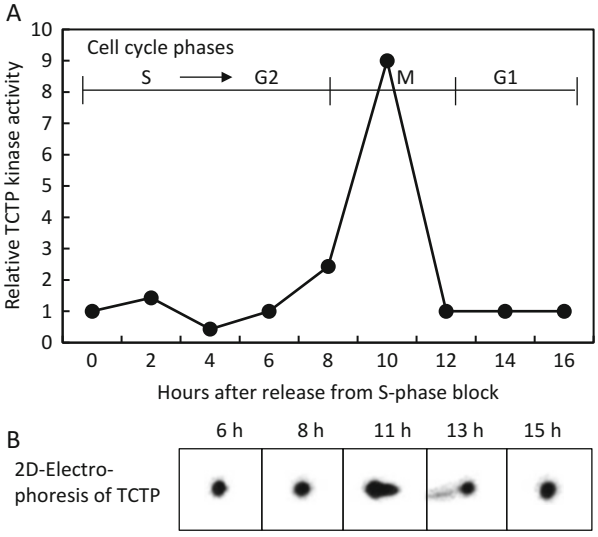

Fig. 4.2 TCTP is phosphorylated by a mitotic protein kinase activity. HeLa cells were synchronised by an S-phase block using aphidicoline. Cell extracts were prepared at the indicated time points after release from the block. The cell cycle phases indicated at the top of the graph were verified by FACS-scan analysis (not shown). (**a**) Cell extracts were tested for TCTP kinase activity by incubating of cell extracts (30 μg total protein) with 1 μg of GST–TCTP fusion protein in the presence of 5 μCi [γ-^{32}P]ATP in 50 mM MOPS buffer, pH 7.2, containing 1 mM DTT, 5 mM $MgCl_2$ and 5 mM p-NPP. The GST–TCTP fusion protein was recovered from the mixture on glutathione-agarose beads and analysed for ^{32}P incorporation by SDS electrophoresis, which was quantified using a phosphoimager. The assay conditions were optimised before, and the incorporation was shown to be specific for TCTP. (**b**) Cells were harvested at the indicated time points after release from the aphidicoline block and analysed by 2D-electrophoresis for TCTP isoforms (Y. Gachet, M. Lee, I. Demalte, J.C. Sanchez and U.A. Bommer, unpublished results)

isoform of TCTP/P23 at the same time (Fig. 4.2b). The protein kinase that catalyses the mitotic phosphorylation of TCTP was subsequently characterised by Frederic Yarm as the mitotic master kinase Plk-1 (Yarm 2002). He also identified the phosphorylation sites for Plk-1 as the serine residues 46 and 64 in the flexible loop of the TCTP protein. Expression of a mutant protein bearing serine to alanine mutations in these sites resulted in a dramatic increase in the number of multinucleated cells, indicating that Plk-1-dependent phosphorylation of TCTP is mediating the detachment of TCTP from the spindle, which in turn is essential for the orderly progression through mitosis. In later studies, TCTP phosphorylation has even been exploited as a marker for Plk-1 activity (Cucchi et al. 2010) and as a potential prognostic marker in testing the efficacy of anticancer drugs (Lucibello et al. 2015).

Localisation of TCTP to the mitotic spindle, particularly the spindle poles, was also reported by other laboratories (Jaglarz et al. 2012; Burgess et al. 2008; Bazile et al. 2009). A very recent paper even demonstrated the importance of TCTP for the *meiotic* spindle in mouse oocytes (Jeon et al. 2016). These authors found that TCTP is predominantly bound to the spindle poles and contributes to the stability of pole microtubules, but not of kinetochore microtubules. TCTP is phosphorylated during meiosis [as also in seen in bovine oocytes (Tani et al. 2007)], and overexpression of a non-phosphorylatable mutant of TCTP led to disturbances of meiotic maturation (Jeon et al. 2016).

A detailed study on plant (*Arabidopsis thaliana; At*) TCTP established that the protein acts as mitotic growth integrator in both plants and animals by controlling the duration of the cell cycle. In this function, the *Arabidopsis* and *Drosophila* proteins are exchangeable in their respective systems (Brioudes et al. 2010). The microtubule-binding activity of AtTCTP has been investigated in yet another paper (Kim et al. 2012a); the binding to actin filaments (Bazile et al. 2009) and identification of an actin-binding site (Tsarova et al. 2011) were also reported for TCTP.

The importance of TCTP in cell cycle progression has been specifically studied in cancer cells. For example, TCTP promoted cell cycle progression in pancreatic cancer cells through stabilisation of the protein kinase Pim-3 (Zhang et al. 2013). In hepatocellular carcinoma (HCC), the oncogene CHD1L was found to drive the overexpression of TCTP, resulting in an increased number of mitotic defects (Chan et al. 2012b). TCTP in turn promoted the degradation of Cdc25C during mitosis, leading to a faster mitotic exit and miss-segregation of chromosomes and consequently to chromosomal instability.

4.2.2.2 Roles for TCTP in Early Development

1. *TCTP in the reproductive system*. The first reports on the role for TCTP in the mammalian reproductive system appeared about 15 years ago. Specifically, the developmental expression of TCTP in the rat and human testes were studied by the group of Sanchez and Hochstrasser in Geneva (Guillaume et al. 2001), and the importance of TCTP as a Ca^{2+}-binding protein in the prostate (Arcuri et al.

2004) and the placenta (Arcuri et al. 2005) were demonstrated by Arcuri et al. A more recent study showed that TCTP is essential for the implantation of embryos in the uterus of mice (Li et al. 2011). An important role for TCTP in egg production in nematodes, such as *C. elegans*, was demonstrated by TCTP knock-down, which severely reduced the number of eggs produced by these worms (Meyvis et al. 2009), consistent with the role of TCTP for meiotic maturation demonstrated in mouse oocytes (Jeon et al. 2016).

2. *TCTP in early development*. The most impressive evidence for the importance of TCTP in early development was provided by TPT1-gene-knockouts in mice, which resulted in embryonic lethality (Susini et al. 2008; Chen et al. 2007a; Koide et al. 2009). The explanation typically given for this effect was 'excessive apoptosis at an early embryonic state' (Susini et al. 2008; Chen et al. 2007a), whereas another report reasons that the lack of TCTP results in an overactivity of the BMP4 (bone morphogenetic protein 4) pathway, which is normally inhibited by TCTP (Koide et al. 2009). The authors of this paper also show that in Xenopus embryos TCTP/fortilin is particularly important for the formation of neural tissue, even in the brain. This is consistent with a very recent report showing that TCTP regulates axon development in the embryonic visual system (Roque et al. 2016).

   The importance of TCTP in early development was also demonstrated in *Drosophila*, where TCTP-knockdown experiments established a role for TCTP in the regulation of cell size and number, organ growth (Hsu et al. 2007) and development (Hong and Choi 2013). Interaction partners of TCTP in this context are the small GTPase Rheb, an upstream regulator of mTOR (mechanistic target of rapamycin), and 14-3-3 proteins (Le et al. 2016). Knockout of TCTP in plants (*Arabidopsis thaliana*) resulted in a male gametophytic phenotype with impaired pollen tube growth. Moreover, TCTP knock-down resulted in severe developmental aberrations, such as slow vegetative growth, reduced leaf expansion and lateral root formation and impaired root hair development (Berkowitz et al. 2008). A recent paper reports on the importance of TCTP (Rp41) for the nodulation and root hair formation in *Robinia pseudoacacia* as another example of TCTP's involvement in plant developmental processes (Chou et al. 2016).

3. *TCTP and pluripotency in somatic cell nuclei and ES cells*. In 2007, several papers documented the involvement of TCTP in early development and the establishment of pluripotency after transplantation of somatic nuclei. Chen et al. monitored the expression of TCTP in the eggs of the cephalochordate *Amphioxus* after fertilisation and found that it is expressed in zygotes and the early, but not the late, cleavage stages (Chen et al. 2007b). Koziol and colleagues reported that TCTP, the gene product of Tpt1, acts as a transcription factor that activates the transcription of oct4 and nanog in transplanted somatic nuclei (Koziol et al. 2007). Oct4 and nanog are transcription factors that are critical for reprogramming of somatic nuclei, when transplanted into oocytes or eggs. Tani et al. observed that phosphorylated TCTP facilitates the first step of somatic cell reprogramming in bovine oocytes (Tani et al. 2007), complementing the study by Koziol. In contrast, another paper reported 5 years later that TCTP

inhibited the Oct4 transcription and also decreased the pluripotency of murine embryonic stem cells (Cheng et al. 2012). In 2010, Johansson and colleagues investigated the interactions of TCTP/tpt1 in mouse embryonic stem cells (ES cells) in more detail. They reported that TCTP interacts with the nucleolar protein nucleolin (Ncl) (Johansson et al. 2010b) and with nucleophosmin (Npm1) (Johansson et al. 2010a), and both these interactions peaked at mitosis, but are independent of TCTP phosphorylation by Plk1. In a third paper, the group also documents the direct interaction of both nucleoplasmin and TCTP with Oct4, independently of each other (Johansson and Simonsson 2010). From these interactions in ES cells, the authors deduce that TCTP has a role in ES cell proliferation and maintenance (Table 4.1).

4.2.3 TCTP in Cell Growth Regulation, Protein Synthesis and Degradation

4.2.3.1 TCTP and Cell Growth Regulation

One of the earliest observations on TCTP is the translational induction of its synthesis upon growth stimulation of mammalian cells (Thomas et al. 1981; Bohm et al. 1989, 1991; Thomas and Thomas 1986). Typically, we observed a four-fold increase of TCTP levels after serum-stimulation of mammalian cells (Bommer et al. 2002, 2015). The involvement of TCTP in cellular growth regulation is documented in various settings. One example, already mentioned above, described the role for TCTP in the regulation of cell size and number, as well as organ growth (Hsu et al. 2007) and development (Hong and Choi 2013) in *Drosophila*. In plants, it was shown that knockout of TCTP resulted in a phenotype with a slow vegetative growth and impaired pollen tube growth (Berkowitz et al. 2008). Another recent paper showed that in the Tobacco plant, TCTP is able to interact with the ethylene receptor histidine kinase-1 and to enhance plant growth through promotion of cell proliferation (Tao et al. 2015).

The regenerating rat liver was frequently used as an experimental model for studying processes of cell growth regulation in rodents. In 2008, Zhu et al. observed that in rat liver, TCTP mRNA levels are transiently up-regulated in the time period up to 12 h after partial hepatectomy, which indicates that the protein is required for tissue growth during liver regeneration (Zhu et al. 2008). This is consistent with a recent report showing that both the expression of intracellular TCTP and the release of TCTP protein into serum were significantly increased in rats after partial hepatectomy, and that enhanced TCTP levels promoted hepatocyte proliferation (Hao et al. 2016).

The influence of TCTP on cellular signalling processes that are involved in the regulation of growth and survival was studied by the group of Kyunglim Lee. They reported that overexpression of TCTP in HeLa cells resulted in tyrosine phosphorylation of the epidermal growth factor receptor and in activation of both the Ras/Raf/

ERK and the PI3K/Akt pathways (Kim et al. 2009b). In a more recent paper, they provided a link to the activity of TCTP in binding to and inhibiting the Na,K-ATPase, which they had observed earlier (Jung et al. 2004). The authors found that TCTP in binding to the third cytoplasmic domain of the Na,K-ATPase results in release and activation of the protein kinase Src and consequently in the activation of the PI3K/Akt and the Ras/Raf/ERK pathways, as well as of additional signalling pathways (Jung et al. 2011). A more recent paper from this group also described a novel activity of (recombinant) TCTP in enhancing the neurotransmitter release from the neurosecretory pheochromocytoma (PC12) cells (Seo et al. 2016).

The signalling pathway most intimately linked to cell growth regulation is the PI3K/Akt-mTORC1 (mechanistic target of rapamycin complex 1) pathway. It is part of a complex signalling network that regulates several anabolic processes, inclusive of protein synthesis (Laplante and Sabatini 2012; Zoncu et al. 2011). In 2007, Hsu et al. published a paper describing TCTP in *Drosophila* as a direct activator of this pathway, acting as a guanine nucleotide exchange factor (GEF) for the small GTPase Rheb, upstream of mTORC1 (Hsu et al. 2007). Consistent with this, reducing *Drosophila* TCTP levels reduced cell size, cell number and organ size, similar to Rheb mutant phenotypes. Subsequently, this group also reported that the 14-3-3 proteins regulate the interaction between TCTP and Rheb, thus playing an important role in regulating organ growth in *Drosophila* (Le et al. 2016). The TCTP–Rheb interaction was further confirmed for the human proteins by molecular modelling studies (Dong et al. 2009). The first description of a NMR structure of TCTP had revealed a similarity of TCTP to the MSS4/DSS4 proteins, which bind to the Rab family of small GTPases (Thaw et al. 2001). Thus, the idea that TCTP acts as a GEF for Rheb appeared attractive, but it remains controversial, since later studies failed to support the results described for Drosophila: We found that reducing TCTP levels did not reproducibly affect mTORC1 signalling in human cells, and we were unable to detect a stable interaction between TCTP and Rheb (Wang et al. 2008). Similarly, Rehmann and colleagues did not detect GEF activity of TCTP for Rheb or any interaction between TCTP and Rheb (Rehmann et al. 2008).

Last but not least, the frequent reports on TCTP overexpression in cancer cells and human tumours (reviewed in Bommer 2012; Acunzo et al. 2014; Chan et al. 2012a; Koziol and Gurdon 2012) and on its down-regulation in the tumour reversion model (Telerman and Amson 2009; Amson et al. 2013) provide additional compelling evidence that TCTP is a growth-promoting protein. These aspects are discussed below, in Sect. 4.3.1.

4.2.3.2 The Involvement of TCTP in Protein Synthesis

Cell and organ growth is dependent on the up-regulation of anabolic pathways, in particular protein synthesis. The core regulatory hub for this regulation is the mTORC1 pathway, which regulates protein synthesis through several mechanisms. For example, mTORC1 enhances the proteosynthetic capacity of the cell through stimulating ribosome synthesis, resulting in an increase in ribosome numbers. This is

achieved through regulation of rRNA synthesis and the selective translational activation of a subset of mRNAs, the 'TOP-mRNAs' whose joint feature is the presence of the 5′-terminal-oligopyrimidine tract (5′-TOP). This group of mRNAs largely comprises those mRNAs coding for components of the translational apparatus, in particular ribosomal proteins and translation factors (Meyuhas and Kahan 2015; Meyuhas 2000). The observations that the mRNA of TCTP also bears a 5′-TOP (Yamashita et al. 2008; Meyuhas 2000) and is regulated through the mTORC1 pathway (Bommer et al. 2015) would suggest that TCTP also participates in the activities (or regulation) of the translational machinery. In fact, as early as 2003, the Telerman group identified translation elongation factor eEF1A and its guanine nucleotide exchange factor eEF1Bβ as TCTP-interacting partners (Cans et al. 2003). TCTP stabilised the GDP form of eEF1A, and impaired the GDP exchange reaction promoted by eEF1Bβ, thereby acting as an inhibitor of the GEF function, in contrast to the activation of the GEF activity of TCTP for Rheb, mentioned above. The interaction of TCTP with eEF1Bβ was later confirmed by Langdon et al. (2004), and a more recent structural analysis of this interaction demonstrated that it represents the most conserved interaction of TCTP, indicating that this might be a primary function of the protein (Wu et al. 2015). A functional screen of proteins associated with ribosomal complexes in yeast identified TCTP as a translation-machinery-associated (TMA) protein, TMA19 (Fleischer et al. 2006). Analysis of yeast mutant strains, deleted in TMA19, revealed that such strains have a reduced rate of protein synthesis and alterations in polysome profiles, lending further support to the notion that TCTP is involved in protein synthesis.

4.2.3.3 TCTP in the Regulation of Protein Degradation

There are a few instances, where TCTP was also reported to be involved in the regulation of protein degradation. Typically, these were examples of degradation of *specific* proteins or participation in autophagy, which either serve to accomplish cell-cycle-dependent processes or otherwise to maintain cellular homeostasis. The involvement of TCTP in the regulation of autophagy in mammalian cells and the underlying mechanism was studied in a recent paper. The authors presented data showing that TCTP interacts with the ATG16L1 complex, which is directly engaged in the autophagy pathway (Chen et al. 2014a). They demonstrated that TCTP positively regulates autophagy through the AMP-activated protein kinase (AMPK) pathway, which also involves mTORC1. This is in contrast to a more recent study, which showed that TCTP inhibits the process of autophagy (see 'Note Added in Proof').

The same group investigated the interaction of TCTP with the tumour suppressor protein 'von Hippel–Lindau protein' (VHL), which functions as an E3 ubiquitin ligase and is involved the degradation of *hypoxia-inducible factor HIF1*. They demonstrated that TCTP binds specifically to the VHL protein and promotes its ubiquitinylation and subsequent degradation, in this way stabilising the HIF1 protein (Chen et al. 2013a). Another important example of TCTP being involved in regulation of protein levels via modulation of protein degradation is the *tumour*

suppressor protein p53. That TCTP overexpression promotes P53 degradation has been demonstrated independently by three groups (Amson et al. 2012; Rho et al. 2011; Funston et al. 2012). It does this by binding to P53-MDM2-containing complexes and inhibiting MDM2 auto-ubiquitination, thereby promoting MDM2-mediated ubiquitination and degradation of P53 (Amson et al. 2012; Funston et al. 2012).

An interesting point is that TCTP was shown to stabilise the proto-oncogenic *protein kinase Pim-3,* which is involved in promoting cell cycle progression and the development of pancreatic cancer (Zhang et al. 2013). In this case, TCTP prevents the degradation of Pim-3 via the ubiquitin–proteasome pathway. Yet another example of a protein that is involved in cell-cycle regulation, and whose levels are modulated by TCTP, is the cell-cycle-dependent *phosphatase Cdc25C*. The ubiquitin–proteasome-dependent degradation of Cdc25C is an important step in mitotic progression. It was shown that in hepatocellular cancer (HCC) this step is promoted by overexpression of TCTP, leading to a faster mitotic exit and consequently to chromosome miss-segregation (Chan et al. 2012b). On the other hand, TCTP itself has been found to be subject to proteasomal degradation after the first embryonic mitosis in *Xenopus laevis* (Kubiak et al. 2008).

The involvement of TCTP with the proteasomal machinery in more general terms has also been demonstrated in two other studies. Rinnerthaler and colleagues showed that in yeast, under heat stress conditions, the TCTP homologue Mmi1 binds to components of the proteasomal complex and to cytoplasmic stress granules. These proteasomal components, to which TCTP colocalises, are typically involved in protecting protein substrates from degradation (Rinnerthaler et al. 2013). Another proteomics study on colon cancer cells identified 27 proteins, whose levels were altered after TCTP knockdown. In particular, components of ubiquitin–proteasome system and proteins involved in the cytoskeleton were affected under this condition (Ma et al. 2010).

4.2.4 Extracellular Functions of TCTP

4.2.4.1 TCTP as Extracellular ‘Signaling Molecule’ in Immune Reactions

Since other chapters of this book will certainly consider the extracellular functions of TCTP in more detail, this aspect of TCTP function will be covered only briefly at this point. In 1995, Susan Macdonald’s group first described the presence of an ‘IgE-dependent histamine-releasing factor (HRF)’ in biological fluids of allergic patients, which was also produced by lymphocytes of atopic children (MacDonald et al. 1995). The molecular characterisation revealed that this protein is identical to TCTP (or p21/p23). Since then, a plethora of papers was published relating to this extracellular function of TCTP/HRF, which I will briefly summarise under the following points. [For a more detailed account, the reader is referred to three recent review articles on this matter (MacDonald 2012a, b; Maeng et al. 2012).]

1. *Release of local signalling molecules from immune cells, triggered by extracellular TCTP/HRF*. The focus of the initial publication, which identified TCTP as HRF, was on the IgE-dependent of histamine release in biological fluids from allergic patients (MacDonald et al. 1995). However, a number of subsequent studies revealed that the 'scope' of TCTP/HRF as an extracellular 'signalling molecule' in immunological reactions is much wider, in that its activity is not IgE-dependent and that it is able to modulate the release of various cytokines in a number of different cell types involved in immune functions (MacDonald 2012a, b). These include B-cells (IL-1, IL-8 release), basophils (IL-4, IL-13 release), T-cells (inhibition of IL-2, IL-13 release), bronchial epithelial cells (IL-8, GM-CSF release) and GM-CSF-primed eosinophils (IL-8 release) (Macdonald 2012b). The potential binding of TCTP to IgE antibodies was a matter of debate (Wantke et al. 1999), but a more recent paper showed that the dimerised form of TCTP is able to bind to a subset of IgE and IgG molecules (Kashiwakura et al. 2012).
2. *Intracellular signalling events induced by TCTP/HRF in immune cells*. In order to gain insight into the intracellular signalling pathways/events that are involved in mediating the TCTP/HRF-dependent release of histamine and cytokines from immune cells, the MacDonald group studied signalling events in basophiles that were triggered by human recombinant TCTP/HRF for histamine release. They found that the activity of the inositol 5′ phosphatase SHIP-1, which inhibits the PI3-kinase signalling pathway, is inversely correlated with the HRF-dependent histamine release in basophils from IgE(+) donors. This finding was corroborated by the demonstration that the PI3-kinase inhibitor Ly294002 also prevented the HRF-dependent histamine release in these cells (Vonakis et al. 2001). In another study, they showed that, in TCTP/HRF-responsive basophils (but not in non-responsive ones), HRF-treatment resulted in phosphorylation of the protein kinase Akt (Vonakis et al. 2008), further confirming that the PI3-kinase pathway is involved in mediating the intracellular events in these type of cells.
3. *Secretion of TCTP, pathways and regulation*. Secretion of TCTP was reported from a number cell types, largely cells involved in the immune system, such as macrophages, dendritic cells and PBMN cells, as well as a range of cancer cells (reviewed in Maeng et al. 2012). This paper also names the different agents that trigger and regulate TCTP release, and it describes the underlying mechanisms for secretion in detail, which I will only briefly summarise here. First, the protein TCTP does not have a signal sequence (Chitpatima et al. 1988; Gross et al. 1989), and no precursor protein for TCTP was detected, meaning that TCTP is not secreted through the classical secretory pathway, via the ER and Golgi apparatus. This was confirmed by the finding that its secretion was insensitive to brefeldin A or monensin, two inhibitors of this pathway (Amzallag et al. 2004). These authors proposed a non-classical pathway for the secretion of TCTP. They showed that TCTP interacts with TSAP6, a transmembrane protein, which is induced by the tumour suppressor protein p53, and that TSAP6 and TCTP co-localise to vesicular structures at the plasma membrane, indicating that TCTP is secreted through an exosomal pathway, guided by TSAP6.

Overexpression of TSAP6 did indeed result in increased TCTP levels in exosome preparations and in enhanced secretion of TCTP (Amzallag et al. 2004), whereas cells derived from TSAP6-deficient mice are severely compromised in the DNA damage-induced p53-dependent exosomal secretory pathway (Lespagnol et al. 2008). Another, also exosome-related pathway for TCTP secretion, was proposed by the Kyunglim Lee's group. –They discovered that TCTP secretion from HEK293 and U937 cells is inhibited by proton pump inhibitors (PPIs), such as omeprazole and pantoprazole, which are inhibitors of the human gastric H(+)/K(+)ATPase and are used in the treatment of gastric ulcers (Choi et al. 2009). Consistent with this, overexpression of the ATPase increased TCTP secretion from these cells, and the authors concluded that this enzyme might facilitate the secretion of TCTP via a non-classical pathway.

4.2.4.2 TCTP Dimerisation and Other Extracellular Roles

The ability of TCTP to self-interact was discovered in Dr. Lee's group as early as in 2000, using the yeast two-hybrid system and co-immunoprecipitation (Yoon et al. 2000). Later, the same group detected the dimerised protein in sera from allergic patients, and they showed that dimerisation is essential for the cytokine-like properties of TCTP/HRF. For dimerisation to happen, the protein had to undergo an N-terminal truncation of about eleven amino acids (Kim et al. 2009a). The group also identified a 7-mer peptide that was able to bind to dimerised TCTP and to inhibit its cytokine-like activity in a cellular assay system and in a mouse model (Kim et al. 2011). Based on their findings and on additional evidence, the authors developed a hypothesis describing two potential mechanisms for the activation (through dimerisation) of extracellular TCTP/HRF to acquire cytokine-like properties (Kim et al. 2013a): (1) A 'spontaneous' mechanism, involving extracellular proteases that trigger N-terminal truncation of the protein and subsequent dimerisation, driven by reactive oxygen species (ROS), which frequently occur in inflammatory processes. (2) Dimerisation by binding to HRF-reactive IgE antibodies, which would confer autoantigen properties to HRF. In each case, only the dimerised TCTP/HRF would bind to the target cell and trigger cytokine release. These ideas are discussed in detail in their review article (Kim et al. 2013a).

Dimerisation of TCTP was reported by other groups in quite different contexts. Gnanasekar et al. characterised the TCTP protein from filarial parasites and found that it occurs in multimeric forms (Gnanasekar et al. 2002). Meshnick and co-workers described TCTP from *Plasmodium falciparum* as a target protein for the antimalarial drug artemisinin (Bhisutthibhan et al. 1999). They observed that dihydroartemisinin may form adducts with both the monomeric and dimeric form of TCTP (Bhisutthibhan and Meshnick 2001). A recent detailed study on ligand binding to human TCTP revealed that binding of haemin to TCTP resulted in a conformational change of the protein and promoted its dimerisation. In contrast, Ca^{2+}-binding resulted in destabilisation of TCTP dimers formed in the presence of haemin (Lucas et al. 2014). The authors propose a 'buffer-like' function for TCTP, since it is able to bind both haemin and Ca^{2+} at higher concentrations. For example, TCTP

may be able to bind intracellular free haemin and keep it in a non-toxic state, preventing the formation of ROS. This paper critically evaluates the earlier literature on Ca^{2+}-binding and on dimerisation of TCTP.

Extracellular 'functions' of TCTP were also described in the context of apoptosis. Apoptotic cell death includes a paracrine function, aimed at promoting tissue repair in the vicinity of the dying cell. To this end, apoptotic cells release nanovesicles containing a set of proteins, different from that of apoptotic blebs. Sirois et al. studied such nanovesicles released from apoptotic endothelial cells and identified TCTP as a prominent anti-apoptotic protein in these vesicles (Sirois et al. 2011). They went on to show that these nanovesicles induce an anti-apoptotic phenotype in vascular smooth muscle cells (VSMCs), and that this activity is abolished in nanovesicles treated with TCTP siRNA. Another, more recent paper studied serum TCTP (fortilin) levels in mice and humans using a newly developed ELISA. The authors found that TCTP/ fortilin levels are significantly elevated in sera from patients with solid cancers, in response to chemo- or radiation therapy, and concluded that TCTP is suitable as a biomarker for apoptosis in vivo (Sinthujaroen et al. 2014).

4.3 Involvement of TCTP in Disease Processes

4.3.1 TCTP in Human Cancer

Other chapters in this book presumably deal with the 'TCTP and Cancer' topic in more detail; I will here just summarise this important part of the TCTP story under three subheadings.

4.3.1.1 Overexpression of TCTP in Human Tumours

As mentioned at the beginning, the name 'translationally controlled tumour protein' was derived from the fact that the cDNA for the first sequence of human TCTP, published in 1989 (Gross et al. 1989), was obtained from a mammary carcinoma. During the ensuing decade, some doubts were voiced on the term 'tumour protein', since TCTP protein and mRNA were detected in essentially all eukaryotic cells and tissues (Thiele et al. 2000; Hinojosa-Moya et al. 2008; Sanchez et al. 1997). However, since the beginning of this century, a substantial body of evidence has been accumulated, demonstrating that TCTP is indeed overexpressed in cancer cells and in human tumours. A number of review articles have summarised these efforts (Telerman and Amson 2009; Bommer 2012; Acunzo et al. 2014; Amson et al. 2013; Chan et al. 2012a; Koziol and Gurdon 2012), and the reader is referred to these for papers reporting overexpression of TCTP in cancer cell lines.

Table 4.2 provides a compilation of the types of human cancers, where overexpression of TCTP was demonstrated in tumour tissues. The table lists only

Table 4.2 TCTP overexpression in human cancers

Cancer type	Methods employed	Clinical associations	References
Brain tumour: Gliomas	Immunohistochemistry, Western blot	High-grade gliomas, poor survival rate	Miao et al. (2013)
	Immunohistochemistry, RT-PCR (mRNA levels)	High-grade gliomas, poor survival rate	Gu et al. (2014)
Breast cancer	Proteomics methods		Deng et al. (2006)
	Immunohistochemistry	Agressive tumours; poor survival rate	Amson et al. (2012)
Colorectal cancer	Northern blot (mRNA)		Chung et al. (2000)
	Proteomics methods		Friedman et al. (2004)
	Microarray analysis (mRNA)		Slaby et al. (2009)
	Immunohistochemistry	(Cellular drug resistance)	Bommer et al. (2017)
	Immunohistochemistry	High grades, metastases, poor survival rate	Xiao et al. (2016)
Kidney and Renal Cell Cancer (RCC)	RT-PCR, Western blot, Immunohistochemistry		Ambrosio et al. (2015)
Leukaemia (CLL)	Immunohistochemistry		Yagci et al. (2013)
Lymphomas (DLBCL, NHL, FL, NK/T-Cell)	Immunohistochemistry		He et al. (2015)
Liver cancer	RT-PCR (mRNA levels)		Zhu et al. (2008)
Hepatocellular carcinoma (HCC)	Immunohistochemistry	Advanced tumours; poor survival rate	Chan et al. (2012b)
Lung cancer	Western blot		Kim et al. (2008b)
NF1-associated tumours	Immunohistochemistry	(Cell tumorigenicity)	Kobayashi et al. (2014)
Neuroblastomas	Immunohistochemistry	Advanced tumours, poor survival rate	Ramani et al. (2015)
Oral cancer	Proteomics methods		Lo et al. (2012)

Osteosarcoma	RT-PCR (mRNA levels)	(Cell tumorigenicity)	Shen et al. (2016)
Ovarian cancer	Immunohistochemistry	Poor prognosis, Cisplatin resistance	Chen et al. (2015)
Pancreatic cancer	Immunohistochemistry	High TCTP and Pim-3 in advanced tumours	Zhang et al. (2013)
Prostate cancer	Immunohistochemistry	Castration resistance	Baylot et al. (2012), Kaarbo et al. (2013)

those papers, which have dealt specifically with one specific type of cancer. There are two additional papers, where the authors have screened a range of cancers for TCTP overexpression, compared to normal tissue, either by western blotting (Tuynder et al. 2002) or using proteomics methods (Kuramitsu and Nakamura 2006). From this screening, it emerged that, apparently, TCTP was not overexpressed in cancers of the stomach and the pancreas (Tuynder et al. 2002; Kuramitsu and Nakamura 2006), of the oesophagus (Kuramitsu and Nakamura 2006) and the cervix (Tuynder et al. 2002), whereas overexpression was confirmed for most other types of cancers investigated. However for pancreatic cancer, a later, more specific study found high TCTP levels, particularly in advanced tumours (Table 4.2). This example shows that for each type of cancer, we have to await more detailed investigations, to confirm (or rule out) TCTP overexpression for a particular cancer type. Currently, the picture emerges that TCTP is overexpressed in a large number of cancer types, certainly in the majority of those investigated so far. Also, where clinical associations have been established, high TCTP levels were typically associated with advanced tumours and poor patient outcomes (Table 4.2).

4.3.1.2 Mechanistic Involvement in Cancer Progression

The importance of TCTP in cancer was originally demonstrated through studies on the 'tumour reversion model' in Adam Telerman's group. This approach investigates the rare events of tumour cells reverting back from the malignant to the normal phenotype (Telerman and Amson 2009). The group showed that TCTP is one of the important proteins, whose expression is down-regulated in this process. Knockdown of TCTP resulted in suppression of the malignant phenotype (Tuynder et al. 2002) and it led to a dramatically increased number of spontaneous revertants (Tuynder et al. 2004). Another group used a proteomics approach to identify proteins that are down-regulated in a reversion model of multiple myeloma. They identified STAT3 and TCTP, among other proteins, as being down-regulated in revertant cells (Ge et al. 2011). The tumour reversion model was instrumental to demonstrate the importance of TCTP in cancer, but the important question remained: What are the mechanisms, through which this protein is able to promote cancer? The following possibilities have emerged from the discussion in recent years.

1. *Anti-apoptotic activity of TCTP*. Overexpression of anti-apoptotic proteins is a common feature and part of the survival strategy of cancer cells. It is therefore not surprising that TCTP is often found to be overexpressed in cancer, alongside other 'classical' anti-apoptotic proteins, such as Bcl-2, Bcl-XL or Mcl-1. Since the discovery of the anti-apoptotic activity of TCTP (fortilin) (Li et al. 2001), several mechanistic aspects of this property have been reported (reviewed in Bommer 2012; Acunzo et al. 2014; Chan et al. 2012a). These were described earlier in Sect. 4.2.1 of this chapter and do not need to be outlined again. However, one of these anti-apoptotic mechanisms ought to be mentioned here, i.e. the antagonism of TCTP to the tumour suppressor protein p53, which is crucial for TCTP to exert its

cancer-promoting activity (Amson et al. 2012; Chen et al. 2011). The cytoprotective role of TCTP in cancer cells is well documented, for example in conditions of oxidative stress (Lucibello et al. 2011), or of treatment with various anticancer drugs, the latter often resulting in chemoresistance of these cells (Li et al. 2001; Jung et al. 2014; Graidist et al. 2004; Bommer et al. 2017; He et al. 2015), which is a frequent problem in cancer chemotherapy.

2. *Promotion of mitosis*. A very specific role of TCTP in cancer promotion was described by Chan et al. in 2012, who studied the chromodomain helicase/ATPase DNA-binding protein 1-like gene (CHD1L), which is a specific oncogene in human hepatocellular carcinoma (HCC) (Chan et al. 2012b). They found that CHD1L acts as a transcriptional activator of TCTP and that the resulting overexpression of TCTP contributed to the mitotic defects of tumour cells. Moreover, TCTP promoted the ubiquitin–proteasome-dependent degradation of the phosphatase Cdc25C during mitotic progression, resulting in a sudden drop of Cdk1 activity in mitosis. The activity of the cyclin-dependent kinase 1 (Cdk1) is normally maintained by Cdc25C and is required for an orderly mitotic exit. The sudden drop of Cdk1 activity caused by TCTP overexpression resulted in a faster mitotic exit and chromosome miss-segregation, which in turn led to chromosomal instability (Chan et al. 2012b). The observation that TCTP is involved in regulating the degradation of Cdc25C through the ubiquitin–proteasome pathway is consistent with other studies reporting a role of TCTP in regulating the ubiquitin–proteasome-dependent degradation of specific proteins (see Sect. 4.2.3). Further support comes from a proteomics study on LoVo colon cancer cells reporting that TCTP knockdown results in the alteration predominantly of components of the ubiquitin–proteasome system (Ma et al. 2010).
3. *TCTP and growth signalling in cancer*. There are several reports describing the effects of alteration of cellular TCTP levels on growth signalling pathways. These were covered earlier (Sect. 4.2.3). Briefly, TCTP overexpression was found to activate the Ras/Raf/ERK, the PLC-γ and the PI3K/Akt growth signalling pathways in HeLa cells (Kim et al. 2009b). Also, Hsu et al. described TCTP in *Drosophila* as an activator of the small GTPase Rheb, an upstream activator of the mTORC1 pathway, and based on this, implicated TCTP in growth regulation (Hsu et al. 2007). However, other follow-up studies could not confirm some of the findings in mammalian cells (Wang et al. 2008; Rehmann et al. 2008). Thus, while some studies indicate that TCTP could act as a growth-regulatory protein, these ideas and the mechanisms involved need further consolidation.
4. *TCTP in specific stages of cancer progression*. Since TCTP is active in promoting cellular growth and proliferation, one would expect the protein also to be involved in the early stages of cancerous growth. Yet, there are not many observations published on TCTP levels specifically in early cancer development. Colorectal cancer (CRC) with its distinct morphology of precancerous lesions, such as adenomas, is amenable for such investigations. Recently, we (Bommer et al. 2017) and a Chinese group (Xiao et al. 2016) demonstrated that indeed TCTP levels (assessed by immunohistochemistry) increase early in CRC, already

at the adenoma stage. This is consistent with our finding that during growth-induction of both HeLa cells and HT29 colon cancer cells, TCTP synthesis is translationally up-regulated through the PI3K/Akt/mTORC1 signalling pathway (Bommer et al. 2015), given the earlier observation that this pathway is activated early in the development of colorectal cancer (Zhang et al. 2009).

Epithelial-to-mesenchymal transition (EMT) of cancer cells is a crucial step in the development of invasiveness and metastasis of tumours. In 2015, Bae et al. published a paper showing that TCTP is able to promote EMT, cell migration and invasiveness (Bae et al. 2015). They also used murine melanoma cells to demonstrate that depletion of TCTP suppresses the development of pulmonary metastasis in a mouse model. Several other studies also demonstrated a role for TCTP in promoting cell migration and invasiveness of cancer cells, and the formation of metastases in animal models. Examples are glioma cells (Jin et al. 2015) and a model for liver metastasis in SCID mice (Chan et al. 2012a); however the cells most frequently studied in this context are those of colorectal cancer. Knockdown of TCTP inhibited proliferation, migration and invasion activities of LoVo colon cancer cells (Ma et al. 2010; Chu et al. 2011). Xiao and co-workers reported that in colon cancer patients, TCTP expression levels were higher in liver metastases, compared to primary tumours (Xiao et al. 2016). They also showed that extracellular TCTP promoted migration and invasiveness of CRC cells in vitro and contributed to distant liver metastasis in vivo. Another example of TCTP being involved in advanced state malignant disease came from a study on prostate cancer (PC). Baylot et al. demonstrated that TCTP is particularly expressed in the castration-resistant form of PC and in metastases of the bone, liver and lymph nodes resulting from this (Baylot et al. 2012). Their results also show that knockdown of TCTP inhibits growth of prostate cancer cells, progression of castration-resistant tumours in mice and reduces their chemoresistance to docetaxel.

5. *Anticancer drug resistance*. A frequent problem in cancer chemotherapy is the development of drug resistance, and some recent reports indicate that TCTP is likely to be involved in this aspect of cancer as well. We have shown that HCT116 colon cancer cells respond to treatment with 5-fluorouracil (5-FU) or with oxaliplatin, two agents frequently used in CRC treatment, with increased TCTP expression. This is probably part of a cellular stress response, since increased TCTP levels protected these cells against the cytotoxicity exerted by these drugs (Bommer et al. 2017). Similarly, the contribution of TCTP (HRF) to the development of cell adhesion and chemoresistance was reported in non-Hodgkin lymphomas (He et al. 2015). Lucibello et al. showed that in breast cancer cells, inhibition of TCTP by dihydro-artemisinin resulted in increased sensitivity to chemotherapy and that phospho-TCTP levels, an indicator of mitotic activity (Yarm 2002), are particularly increased in breast tumours that are resistant against treatment with the trastuzumab antibody (Lucibello et al. 2015).

Reports on the involvement of TCTP in anticancer drug resistance started to appear as early as 2000. Sinha and co-workers performed a proteomics analysis on human melanoma cell lines that were resistant to drugs like vindesine,

cisplatin and etoposide. They identified TCTP as one of four proteins overexpressed in those cell lines, compared to their no-resistant parental cells (Sinha et al. 2000). Fujise's laboratory demonstrated TCTP (fortilin)-dependent drug resistance against etoposide (Li et al. 2001) and 5-FU (Graidist et al. 2004) in U2OS cells. In a more recent study, Kyunglim Lee's laboratory explored the mechanism underlying the TCTP-dependent resistance against etoposide in HeLa cells. They demonstrated that TCTP interacts with the apoptotic protease-activating factor (Apaf-1), associates with the apoptosome and inhibits activation of caspase 3 and execution of apoptosis (Jung et al. 2014).

4.3.1.3 TCTP as an Anticancer Target

Given the well-established role of TCTP in cancer as summarised in this section, it is not surprising that the idea of exploring TCTP as an anticancer target protein is not new, and this interesting topic has already been covered in six review articles (Telerman and Amson 2009; Bommer 2012; Acunzo et al. 2014; Amson et al. 2013; Efferth 2005, 2006). Here I will briefly summarise these efforts, according to the groups of drugs investigated to target TCTP:

1. *Artemisinin*: Since the early discovery that TCTP of *Plasmodium falciparum* is a target protein of the antimalarial drug artemisinin (Bhisutthibhan et al. 1998), this drug interaction has been studied in more detail (Chae et al. 2006). Artemisinin not only displays antimalarial activity but was also found to be a potent anticancer agent in cellular assay (review in Efferth 2005), and screening for potential targets in this context has confirmed that TCTP is indeed a target for this drug (Efferth 2005, 2006). The interaction of artemisinin with TCTP was then studied in cancer cells, and it was found that drug treatment results in degradation of TCTP (fortilin) via the ubiquitin–proteasome pathway (Fujita et al. 2008). More recent publications described proof-of-principle investigations for the use of artemisinin as an anticancer drug in cellular models of lung cancer (Liu et al. 2014), of Neurofibromatosis type 1 (NF1)-associated tumours (Kobayashi et al. 2014) and of breast cancer (Lucibello et al. 2015). Specifically, the latter report demonstrated that dihydroartemisinin enhances the anticancer effect of doxorubicin in triple-negative breast cancer cells and acts synergistically with the antibody Trastuzumab, which is used for the treatment of HER2/neu positive breast cancers, to induce apoptosis of tumour cells.
2. *Antihistaminics and antidepressants*. Based on the identification of TCTP as histamine-releasing factor HRF (MacDonald et al. 1995), the Telerman laboratory tested a panel of antihistaminic drugs for their effect on human leukaemia and breast cancer cells (Tuynder et al. 2004). Of these ones, hydroxyzine and promethazine displayed growth-inhibiting activity on these cells. These antihistaminics are structurally related to the antidepressants sertraline and thioridazine, which also inhibited tumour growth, both in vitro and in vivo (Tuynder et al. 2004). All these drugs bind to TCTP and disrupt its interaction with other partner proteins, eventually leading to increased release of the protein from the cell and to

lowered intracellular TCTP levels (Telerman and Amson 2009). Since the demonstration of the reciprocal repressive feedback loop between TCTP and the tumour suppressor P53 by the same laboratory (Amson et al. 2012), the mechanism of action of these drugs can be described in more detail as follows (Amson et al. 2013): Binding of sertraline and thioridazine to TCTP prevents its binding to MDM2 and consequently the destabilisation of P53. The resulting increased P53 levels lead to additional transcriptional inhibition of TCTP expression. An additional mechanism is based on the finding that both sertraline (Lin et al. 2010) and thioridazine (Kang et al. 2012) inhibit the mTOR signalling pathway. Blocking this pathway in itself will inhibit TCTP expression, since TCTP mRNA translation is regulated through the mTOR pathway (Bommer et al. 2015). In *Drosophila*, TCTP was described as a positive regulator of the mTOR pathway via the small GTPase Rheb (Hsu et al. 2007); it is therefore possible that TCTP and mTOR are in a positive feedback loop (Kobayashi et al. 2014), which would be disrupted by treatment with sertraline or thioridazine. In a very recent paper, two additional antihistaminic drugs, buclizine and levomepromazine, were reported to inhibit cancer cell growth by binding to TCTP and by inducing cell differentiation (Seo and Efferth 2016).

3. *Antisense oligonucleotides (ASOs) and anti-TCTP peptide*. Synthetic agents that target TCTP were first used by Baylot and colleagues, who patented an ASO against TCTP (Baylot et al. 2012). In their study, they used a mouse model to show that treatment with the TCTP-ASO inhibits tumour growth in castration-resistant prostate cancer, enhances docetaxel chemotherapy and delays cancer progression in vivo. This effect is associated with an increase in P53 levels (Acunzo et al. 2014; Baylot et al. 2012). In addition, recently a peptide aptamer (WGQWPYHC) targeting TCTP was tested and found to display specific cytotoxicity towards TCTP expressing tumour cells, without affecting normal cells (Kadioglu and Efferth 2016).

In summary, both existing drugs that are in use for treatment of other disease groups (antimalarials, antihistaminics, antidepressants) and synthetic agents designed to specifically target TCTP show promising results in proof-of-concept studies as potential approaches for anticancer treatment.

4.3.2 Participation in Immunological Reactions

Since the discovery of TCTP as an 'IgE-dependent histamine-releasing factor (HRF)' in biological fluids of allergic patients (MacDonald et al. 1995), many papers have been published, relating to the involvement of TCT/HRF in allergic diseases and other activities of the immune system. The molecular and cellular aspects of these extracellular activities of TCTP/HRF have been summarised in the preceding Sect. 4.2.4. Here, I will just touch on some of the clinical aspects, based on the reviews and some recent papers:

As mentioned in Sect. 4.2.4, the extracellular function of TCTP/HRF consists of a cytokine-like activity, in that it is able to trigger several types of immune cells to release cytokines or other signalling molecules, not only the IgE-dependent histamine release from basophils, as described originally (reviewed in Macdonald 2012b; Kawakami et al. 2012). Although the association of TCTP/HRF with human allergic disease has been widely accepted, its exact role in the clinical context still awaits further clarification (Kawakami et al. 2012). Several small-group clinical investigations have established a correlation between the TCTP/HRF status and a range of clinical parameters typical in allergic diseases. Such clinical parameters include the following: (1) the sensitivity of basophils from a subpopulation of allergic donor patients to TCTP/HRF, (2) the intensity of symptoms in the late phase reaction of the allergic response, (3) bronchial hyper-reactivity and sensitivity to histamine, (4) the clinical status of food allergy and atopic dermatitis (reviewed in Macdonald 2012b). However, not all clinical studies were able to detect such correlations (see, e.g. Budde et al. 2002). The observation that the TCTP proteins of two highly allergenic fungal species [*Cladosporium herbarum* (Rid et al. 2008) and *Alternaria alternata* (Rid et al. 2009)] are able to cause histamine release from human basophils and to compete with human HRF is also of interest in this context.

Apart from establishing a clinical correlation, the next question is whether there is indeed a causal relationship between HRF/TCTP levels (or activity) with the disease symptoms. The generation of an inducible transgenic mouse model with overexpressing HRF/TCTP targeted to lung epithelial cells was a first step to address this question. These mice have increased HRF protein levels both in the lung epithelium and extracellularly in the BAL fluid; moreover, HRF exacerbates the allergic, asthmatic responses in these animals after ovalbumin challenge (Yeh et al. 2010). An inherent problem for delineating the precise role of TCTP/HRF in the allergic disease processes lies in its multifunctionality that entails many intracellular roles in addition to the extracellular ones, which makes it difficult to exclude off-target effects (Kawakami et al. 2012).

There was some debate in the literature, whether or not TCTP/HRF binds directly to IgE antibodies and in this way triggers histamine release from mast cell and basophils (Kawakami et al. 2012). A recent detailed study demonstrated that a subset of both IgE and IgG antibodies are able to bind TCTP/HRF (Kashiwakura et al. 2012). Dimerisation of TCTP as a prerequisite for its cytokine-like activity was shown before (Kim et al. 2009a, 2013a). Kawakami and colleagues demonstrated in their paper that it is indeed dimerised TCTP/HRF that binds to these antibodies. They mapped the binding site on TCTP and used corresponding peptides to block its interaction with the 'cognate' IgE antibody. They also showed that these Ig-interacting TCTP/HRF peptides inhibited IgE/HRF-induced mast cell activation in vitro and other allergenic symptoms in a mouse model in vivo (Kashiwakura et al. 2012). This finding demonstrates that TCTP/HRF has a proinflammatory role in asthma and skin hypersensitivity and also that it can be considered a potential therapeutic target. This idea was not entirely new, since just before, Dr. Lee's group identified a 7-mer peptide that binds

preferentially to dimerised TCTP and is able to block IL-8 release from BEAS-2B cells triggered by dimeric TCTP. This peptide reduced eosinophil infiltration and other symptoms in a mouse rhinitis model (Kim et al. 2011), and it is non-toxic (Kim et al. 2013b). These two examples indicate that TCTP/HRF may indeed be a valid target for the treatment of symptoms in allergic disease.

4.3.3 TCTP in Lower Animals and Parasitic Infections

There is a large number of reports on TCTP proteins and their biological function in lower animals and plants. The high degree of conservation was mentioned in the introduction (for review see Hinojosa-Moya et al. 2008). Here, I will focus on those papers, which deal with the involvement of such TCTP proteins in infectious or immune response processes or are otherwise potentially involved in human disease.

4.3.3.1 TCTP in Protozoans

The first TCTP protein described in a protozoan was from *Plasmodium falciparum (Pf)*, one of three parasites causing malaria. It was discovered as one of the target proteins for the antimalarial drug artemisinin (Bhisutthibhan et al. 1998). This paper demonstrated that TCTP reacts with artemisinin in situ and in vitro in the presence of haemin and that it binds haemin itself. The interactions of Pf-TCTP with artemisinin (Chae et al. 2006) and of human TCTP with haemin (Lucas et al. 2014) were subsequently studied in more detail, as was the subcellular location and calcium-binding activity in *Plasmodium* (Bhisutthibhan et al. 1999).

The role of malarial TCTP in the host–parasite interaction was studied in three papers: MacDonald et al. showed that malarial TCTP is secreted by the parasite and can be detected in the blood of infected individuals (MacDonald et al. 2001). They also showed that, like human TCTP/HRF, Pf-TCTP is able to stimulate histamine release from basophils and IL-8 secretion from eosinophils, but is much less efficient to do so. Thus, malarial TCTP could compete with human HRF for the binding sites on the immune cells and in this way dim the host immune response. Similarly, another paper demonstrated that Pf-TCTP is incorporated into mouse splenic B-cells at a much higher rate than human TCTP, but has a much lower proliferative effect on B-cells than its human counterpart (Calderon-Perez et al. 2014). A recent study even explored the potential of malarial TCTP as a vaccine to reduce parasitaemia in mice. In two trials, a significant reduction in parasitaemia in the early stages of infection was observed in BALB/c mice (Taylor et al. 2015).

4.3.3.2 TCTP in Parasitic Worms

Reports on the biology of TCTP in parasitic worms typically revolve around the topic of cyto-protection, defence and host–parasite interaction. Two papers characterise the calcium-binding properties of TCTP from the filarial parasites *Brugia malayi* and *Wuchereria bancrofti* (Gnanasekar et al. 2002) and from *Schistosoma mansoni* (Rao et al. 2002). They detected the parasite TCTP protein in the bloodstream of infected mice and described its histamine-releasing activity and the promotion of allergic inflammatory responses associated with filarial infections in these mice. The same group also characterised *Brugia malayi* TCTP as an antioxidant protein (Gnanasekar and Ramaswamy 2007) and TCTP from *Schistosoma mansoni* as a heat-shock protein (Gnanasekar et al. 2009). Similarly, in two *Trichinella* species, TCTP was reported to be heat-induced (Mak et al. 2001, 2007), indicating that it is involved in cyto-protection under heat-shock conditions.

A study on TCTP in two nematode species, *Ostertagia ostertagi*, a parasitic nematode in cattle, and in the free-living nematode *Caenorhabditis elegans* revealed that in both species, TCTP was predominantly located in the eggs of the animals (Meyvis et al. 2009). Interestingly, knock-down of TCTP in *C. elegans* reduced the number of eggs laid by the hermaphrodite in the F0 generation by 90%, indicating that TCTP plays a pivotal role in nematode reproduction.

4.3.3.3 TCTP in Crustaceans and Other Waterborne Animals

Among crustaceans, the TCTP protein most widely studied was in several species of shrimp, usually by researchers from the Southeast Asian region, predominantly Thailand. This is because the shrimp industry plays a substantial role in the economy of this region. One of the major threats to shrimps is the white spot syndrome virus (WSSV), and several papers show that shrimp TCTP is involved in immune defence of the animals against the virus. One of the earliest papers on shrimp TCTP reported already that TCTP levels are severely down-regulated in the advanced stages of viral infection, compared to early infection stages and uninfected animals (Bangrak et al. 2004). Subsequently, the same group demonstrated that injection of shrimps with recombinant TCTP/fortilin after infection with WSSV resulted in 80–100% survival, and it severely reduced the virus load (Tonganunt et al. 2008). Consistent with this, TCTP/ fortilin of the shrimp *Penaeus monodon* inhibited the expression of early and late genes of the WSSV virus in an insect cell model (Nupan et al. 2011). The group also identified a novel binding partner to TCTP/fortilin, fortilin-binding protein (FBP1), which might be involved in the immune defence as well (Panrat et al. 2012).

Recently, a Chinese group working on the TCTP protein of another shrimp species, *Litopenaeus vannamei*, reported that TCTP expression was significantly up-regulated at 16 h and 48 h following infection with the WSSV virus. Silencing of TCTP with dsRNA led to a significant increase in WSSV loads (Wu et al. 2013). Yet another Chinese group studied the TCTP protein from the sea cucumber

Stichopus monotuberculatus. They demonstrated the anti-oxidation and heat-shock protein properties of recombinant TCTP protein, and their data suggested that the sea cucumber TCTP may also play an important role in the innate immune defence against bacterial and viral infections (Ren et al. 2014). Most recently, the characterisation of the TCTP protein of the scallop *Chlamys farreri* (Cf) was published (Jia et al. 2017). Its expression levels are highly regulated during embryonic development of the mollusc, and in response to stimulation with PAMPs (pathogen-associated molecular patterns). Recombinant CfTCTP could induce the release of histamine from BT-549 cells. These results indicate that TCTP plays a pivotal role in the embryonic development and immune protection of scallops.

4.3.3.4 TCTP in Arthropods

Similar to the situation in shrimps, the TCTP protein of the silkworm *Bombyx mori* (Bm) has attracted special attention, particularly from Chinese researchers, although the initial characterisation of the mRNA and the gene structure of BmTCTP was published by a Japanese group (Lee et al. 2004). Later, the Chinese group studied the role of BmTCTP in gut immunity of the silkworm in more detail (Wang et al. 2013). They found that BmTCTP is produced in intestinal epithelial cells and released into the lumen of the gut. The production increases at early time points during oral microbial infection, but declines later. BmTCTP acts as a multi-ligand-binding protein; it also functions as an opsonin that promotes phagocytosis of microorganisms. TCTP induces the production of an antimicrobial peptide via a signalling pathway, which involves activation of ERK. The authors conclude that TCTP is a dual-function protein involved in both the cellular and the humoral immune response of the silkworm. In support of this, the group recently studied the effect of silencing of TCTP by RNAi in a transgenic silkworm (Hu et al. 2015). They reported that the antimicrobial capacity of the silkworm decreased, since the expression of the gut antimicrobial peptide was not sufficiently induced during microbial challenge. This led to the suppression of the innate intestinal immunity, as result of RNAi-mediated knockdown of TCTP.

In summary, the results described in the last two sections show that TCTP is involved not only in cellular defence mechanisms, such as protection against oxidation or heat-shock, but also in innate immunity, of both mammals and the lower taxa of the animal kingdom. A recent, very unusual addition to the various biological roles of the TCTP protein represents a more ‘aggressive’ one, i.e. the participation in the deadly cocktail of spider venoms. Two papers reported that translationally controlled tumour protein is a component of the venom from the brown spider *Loxosceles intermedia* (Gremski et al. 2014; Sade et al. 2012). Another one investigated the spit (used to ‘glue’ the prey to a solid surface) and the venom of the spider *Scytodes thoracica* using transcriptomic and proteomic analyses. In these secretions, they detected TCTP alongside 19 different groups of toxic peptides (Zobel-Thropp et al. 2014).

4.3.4 TCTP in Other (Patho)physiological Processes

Apart from being involved in cancer and, as an extracellular protein, in inflammatory and immune reactions, TCTP also participates in other physiological processes and, if deregulated, in pathologic derailments of these. Known examples will be summarised in this section.

4.3.4.1 Metabolic Regulation and Diabetes

About five years ago, we studied the regulation and protective role of TCTP in pancreatic β-cells and demonstrated that TCTP levels are up-regulated in response to stimulatory glucose concentrations, but down-regulated in stress conditions induced by fatty acids (palmitate). Overexpression of TCTP prevented cell death induced by palmitate (Diraison et al. 2011). These results imply that TCTP protects β-cells against stress induced by hyperglycaemia and by high concentrations of fatty acids. More recently, Tsai and colleagues studied the effect of TCTP levels on β-cell proliferation in mice (Tsai et al. 2014). They found that (1) TCTP expression levels are increased under conditions of enhanced β-cell proliferation, i.e. in the perinatal development period and in insulin-resistant states (induced by high-fat diet); (2) TCTP-knockout resulted in decreased β-cell proliferation and cell mass, and in reduced insulin production, eventually leading to hyperglycaemia. Together, these two papers highlight the importance of TCTP for maintaining the homeostasis of pancreatic β-cells and reducing the risk of developing hyperglycaemia and eventually type 2 diabetes.

Whilst in the case of β-cells, the growth-promoting activity of TCTP helps to maintain metabolic homeostasis; in other cell types it may contribute to pathological alterations caused by diabetes. An example is provided through a paper by Kim et al. on podocyte hypertrophy, one of the renal pathologies induced by diabetes (Kim et al. 2012b). They reported that TCTP levels are increased in the glomeruli of diabetic mice, compared to control animals. Knockdown of TCTP led to reduced activity of the mTORC1 pathway in diabetic glomeruli; it reduced the size of the podocytes and prevented the development of diabetic nephropathy.

Very recently, Goodman and colleagues studied the involvement of TCTP and the mTOR signalling pathway in physiological models of skeletal muscle hypertrophy and atrophy (Goodman et al. 2017). Their results show that TCTP and mTOR signalling are up-regulated in both hypertrophy and atrophy of skeletal muscle. The increase in TCTP observed under these conditions occurred in part via an mTOR-dependent mechanism. However, the overexpression of TCTP was not sufficient to activate mTOR signalling. The authors provide preliminary evidence to show that TCTP may act through inhibiting protein degradation, rather than activation of protein synthesis.

4.3.4.2 Blood Circulation

There are also pathologies of the cardiovascular system that are being promoted through TCTP. First, a paper by Kyunglim Lee's group reported that a transgenic mouse overexpressing TCTP develops systemic hypertension (Kim et al. 2008a). These authors had previously shown that TCTP inhibits the Na/K-ATPase, and they proposed that promotion of hypertension by TCTP operates through this mechanism.

A different disease, despite its similar name, is pulmonary arterial hypertension (PAH). It is a lethal disease, caused by excessive proliferation of pulmonary vascular endothelial cells. The hereditary form (HPAH) is often caused by mutations in the bone morphogenetic protein receptor type 2 gene (BMPR2). Lavoie et al., through a proteomics screen, comparing HPAH patients with BMPR2 mutations with healthy control subjects, identified TCTP as one of 22 significantly altered proteins (Lavoie et al. 2014). They reported that TCTP is markedly up-regulated in remodelled blood vessels of complex lesions in lungs from patients with PAH. Silencing of TCTP expression increased apoptosis and abrogated the hyperproliferative phenotype of epithelial cells from patients with HPAH.

Also in the case of atherosclerosis, TCTP seems to play a disease-promoting role, albeit through a different mechanism. Ken Fujise's group has generated a mouse model with heterozygous deficiency of TCTP/fortilin in a background of hypercholesterolemia, which develops atherosclerotic characteristics, similar to those in humans (Pinkaew et al. 2013). Studying this animal model, they arrived at the conclusion that TCTP/fortilin acts by reducing apoptosis in macrophages, one of the main players in the development of atherosclerosis. On the other hand, based on experiments using TCTP overexpression in ApoE-knockout mice, Kyunglim Lee's group proposed that TCTP enhances the severity of atherosclerotic lesions through the induction of hypertension (Cho et al. 2012).

Taken together, the examples of TCTP's involvement in diseases given in Sect. 4.3.4 are by and large based on the growth-promoting effect of TCTP in quite different cellular settings. In one case (pancreatic β-cells), the net effect of TCTP is beneficial; in most other cases, it is disease promoting. All examples—inclusive of cancer—show that, whilst TCTP is generally a cytoprotective protein, its excessive up-regulation is likely to cause disease. Therefore, understanding the regulation of TCTP at the cellular level (see following section) is essential for exploring the mechanisms of such diseases and eventually for our ability to modulate them.

4.4 Regulation of Cellular TCTP Levels

4.4.1 Cell Physiologic Conditions That Result in Regulation of TCTP Levels

Considering the sheer number and range of cell biological processes TCTP is involved in (see Sect. 4.2), it is not surprising that cellular levels of the protein are highly regulated, in response to many different environmental cues and also through a variety of regulatory mechanisms. Presumably, a large number of researchers, who today work on TCTP, originally discovered the protein either in an interaction screen (see Table 4.1), or in search of genes/proteins that are regulated in defined alterations of physiologic conditions, or during transition to a disease state. Typically, TCTP is among those proteins, which display the most prominent changes.

Table 4.3 provides a list of publications, which reported alterations of intracellular TCTP levels in response to altered cell physiologic conditions. The Table lists the type of signals for adaptation ('Stimulus'), the cellular system observed and the likely regulatory mechanism involved. Within the scope of this chapter, it is impossible to discuss each of these cases, and the reader is referred to the individual reference for further details. For this table, I have included only those specific cases of cancer, where a specific mechanism of TCTP up-regulation has been described. The other examples of TCTP overexpression in cancer are listed in Table 4.2.

Two general points emerge from this compilation: (1) The type of physiological settings/adaptations that result in regulation of cellular TCTP levels largely correspond to those conditions, where TCTP was shown to be involved, either as promoting or as protective protein (compare Sect. 4.2.1 to 4.2.3). (2) A whole range of regulatory mechanisms may be involved in regulating TCTP levels, i.e. transcriptional or translational regulation, or stability regulation of TCTP mRNA or protein. However, since not all of the papers listed went into detail to prove or disprove the one or other option, the overall picture is incomplete and may look biased towards transcriptional or translational control. Further work will be necessary to refine this list and confirm or disprove certain types of regulatory mechanisms.

4.4.2 Mechanisms Involved in Regulation of Cellular TCTP Levels

In this section, I will only discuss those papers which explored the *mechanisms* and signalling pathways that underlie the adaptation of TCTP levels in specific cell physiologic settings, not those which just report altered TCTP protein or mRNA levels.

Table 4.3 Cell physiologic conditions resulting in alterations of TCTP levels

Stimulus	Cell/tissue type	Change	Mechanism involved	References
Growth signals: Serum	Swiss 3T3 cells	Up	Translational control	Thomas et al. (1981), Thomas and Thomas (1986)
Serum	Ehrlich ascites cells	Up	Translational control	Bohm et al. (1989, 1991)
Serum	NIH 3T3 cells	Up	Translational control (eIF4E)	Bommer et al. (1994)
Serum	HeLa, HT29 cells	Up	Translational (mTORC1)	Bommer et al. (2015)
Liver regeneration	Rat liver	Up	Transcription activation	Zhu et al. (2008)
Serum starvation	MEF cells	Down	Translation inhibition (PKR)	Bommer et al. (2002)
Hypertrophy/ Atrophy	Mouse muscle	Up	Translational (mTORC1)	Goodman et al. (2017)
Cell cycle: Mitotic exit	Xenopus embryos	Down	Proteasomal degradation	Kubiak et al. (2008)
Cell signalling: Phorbol ester	T24 carcinoma cells	Up	Transcription activation	Andree et al. (2006)
M-CSF	Mouse macrophages	Up	Increased mRNA and protein	Teshima et al. (1998)
Cell differentiation	Mouse erythro-leukaemia cells	Up	Transcription activation	Yenofsky et al. (1983)
Nutrients: Glucose	Pancreatic β-cells	Up	TCTP protein levels	Diraison et al. (2011)
Fatty acids	Pancreatic β-cells	Down	TCTP protein levels	Diraison et al. (2011)
Ammonium starvation	Yeast	Down	Transcription repression	Bonnet et al. (2000)
Heat shock	Prostate cancer cells	(Up)	Hsp27 protects TCTP protein	Baylot et al. (2012)
	Schistosoma; human	Up	Transcription activation	Gnanasekar et al. (2009)
	Trichinella spiralis	Up	Transcription activation	Mak et al. (2001)
	Trichinella pseudospiralis	Up	Translational control	Mak et al. (2007)
Oxidative stress: strong: ATO	Cancer cells	Down	TCTP protein levels	Lucibello et al. (2011)
(mild) H_2O_2	Cancer cells	Up	TCTP protein levels	Lucibello et al. (2011)
(mild) H_2O_2	Human keratinocytes	Up	Transcription activation (VDR)	Rid et al. (2010)
H_2O_2	Plant stresses	Up	Transcription activation	Chen et al. (2014b)

(continued)

Table 4.3 (continued)

Stimulus	Cell/tissue type	Change	Mechanism involved	References
Ca(2+)-Stress: A23187; Thapsigargin	Cos-7 cells	Up	Transcription and translation	Xu et al. (1999)
A23187; Thapsigargin	MEF cells; β-cells	Down	Translation inhibition (PKR)	Bommer et al. (2010)
Thapsigargin	Pancreatic β-cells	Down	TCTP protein levels	Diraison et al. (2011)
DNA damage: γ-Rays	Human cells	Up	TCTP protein levels	Zhang et al. (2012)
Specific cancer types[a]	Hepatocellular cancer (HCC)	Up	Transcription activ. (CHD1L)	Chan et al. (2012b)
	Oral cancer cells	Down	mRNA repression (miRNA-27b)	Lo et al. (2012)
	NF1-associated Tumours	Up	Translational (mTORC1)	Kobayashi et al. (2014)
Alzheimers; Down Syndrome	Brain regions	Down	Protein levels decreased	Kim et al. (2001)
Apoptotic factors: P53	Murine cells	Up	Transcription activation	Chen et al. (2013b)
P53	Breast cancer cells	Down	P53 inhibits transcription	Amson et al. (2012)
P53	RTL6 cells; Mouse erythro-leukemia cells	Down	P53 reduces TCTP protein	Tuynder et al. (2002), Bommer et al. (2010)
Depletion of Mcl-1	U2OS cells	Down	Protein degradation	Zhang et al. (2002)
Heavy metals: Copper (Cu)	Calu-6 and Cos-7 cells	Up	Transcription and translation	Schmidt et al. (2007)
Cobalt, Nickel	Calu-6 and Cos-7 cells	Up	mRNA stabilisation	Schmidt et al. (2007)
Cd, Cu, Pb, Zn	Earth worms	Up	Transcription activation	Sturzenbaum et al. (1998)
Uranium nitrate	Mouse kidneys	Up	Transcription and translation	Taulan et al. (2006)
Aluminium stress	Soybean cultivars	Up	Transcription activation	Ermolayev et al. (2003)
Salt stress	Cassava plant	Up	Transcription activation	Santa Brigida et al. (2014)
Mercury Stress	Rice roots	Up	TCTP protein levels	Wang et al. (2012)
Toxins: Dioxin	Mouse ES cells	Up	Transcription activation	Oikawa et al. (2002)
Dioxin	Calu-6 and Cos-7 cells	Up	Transcription activation	Schmidt et al. (2007)
Naphthenic acids	Earth worms	Up	Transcription activation	Wang et al. (2015)

(continued)

Table 4.3 (continued)

Stimulus	Cell/tissue type	Change	Mechanism involved	References
Drugs: 5-Fluorouracil	Colon cancer cells	Up	Translational (mTORC1)	Bommer et al. (2017)
Oxaliplatin	Colon cancer cells	Up	Translational (mTORC1)	Bommer et al. (2017), Yao et al. (2009)
Ursolic acid	Hepatocellular carcinoma cells	Down	Reduced PI3K signalling	Chuang et al. (2016)
Dihydro-artemisinin	Several cell lines	Down	Proteasomal degradation	Fujita et al. (2008)
Dihydro-artemisinin	Breast cancer cells	Down	Proteasomal degradation	Lucibello et al. (2015)
Sertraline, Thioridazine	Breast cancer cells	Down	Increased p53; mTOR inhibition	Amson et al. (2013)

[a]Only those cancer types are listed, where the mechanism of TCTP regulation has been explored

4.4.2.1 Transcriptional Regulation of TPT1 Gene Expression

The most comprehensive analysis of the gene structure and transcriptional regulation of the mammalian TPT1 gene came from the Thiele laboratory in Berlin. The gene and mRNA structures were described in Sect. 4.1.2; here I will just summarise the results on mechanisms of transcriptional regulation of TCTP expression. Andree et al. (2006) performed predictions of potential transcription factor-binding sites in the 5′-flanking region of the TPT1 gene of five mammalian species, which revealed the conservation of a cluster of five such binding sites within the first 170 nucleotides 5′-terminal to the transcription start site of these genes. These comprised two binding sites each for the transcription factors ETS1 and CREB and one binding site for MZF1. In this paper, they confirmed experimentally that TCTP expression is indeed regulated by phorbol ester (PMA) and forskolin through the cAMP-PKA signalling pathway via transcription factor CREB.

Other confirmed examples of transcriptional regulation of TCTP synthesis include the following:

Differentiation of mouse erythroleukaemia (MEL) cells is induced by treatment of cells with DMSO. It belongs to the very early observations on TCTP (P21) mRNA that its synthesis increases early in this process, even though its translation rate decreases after exposure to DMSO (Yenofsky et al. 1983).

Other examples of specific *transcriptional regulation of the TPT1 gene* are *relevant to cancer*: (1) The tumour suppressor protein P53 acts as a transcription factor and, as an antagonist to TCTP, it binds to a p53-response element upstream of the TPT1 gene and represses its transcription in human cells (Amson et al. 2012). This inhibitory activity is alleviated in cancers, which bear mutations in the p53

gene, as it is frequently the case. (2) In hepatocellular cancer (HCC), a transcription factor called CHD1L has been identified as a specific oncogene. CHD1L binds to the promoter region of the TPT1 gene and activates its transcription (Chan et al. 2012b). (3) Transcriptional regulation of TCTP by HIF-1α was reported by Xiao et al. in colon cancer cells (Xiao et al. 2016). (4) In rat liver regeneration, a model of actively proliferating tissue, the expression of TCTP mRNA is transiently up-regulated, from 3 to 12 h after partial hepatectomy (Zhu et al. 2008).

There are also examples of *TCTP being transcriptionally regulated in stress conditions*: (1) Mild oxidative stress induced by hydrogen peroxide was reported to induce transcription activation of TCTP expression through the vitamin D3 receptor (VDR) in keratinocytes (Rid et al. 2010) and plants (maize) under flood stress conditions (Chen et al. 2014b). (2) Transcriptional induction of TCTP synthesis by heavy metals has been observed very early in earthworms (Sturzenbaum et al. 1998). In this case, copper and cadmium led to the highest rates of TCTP mRNA synthesis. A more detailed study on the regulation of TCTP by heavy metals was subsequently performed in the Thiele laboratory (Schmidt et al. 2007). They found that copper induced TCTP synthesis at both the transcriptional and the translational level, whereas cobalt and nickel seem to result in TCTP mRNA stabilisation. These authors also showed that the potent toxin dioxin (TCDD) transcriptionally activates TCTP synthesis in human and Calu-6 and Cos-7 cells, which mirrors an earlier report on mouse embryonic stem cells (Oikawa et al. 2002).

Further examples of transcriptional activation of TCTP synthesis are given in Table 4.3.

4.4.2.2 Translational Regulation of TCTP Synthesis

The early demonstration that TCTP is a translationally controlled protein was based on the following evidence: (1) The rate of synthesis of the proteins 'Q23' (Thomas et al. 1981) and 'P23' (Bohm et al. 1989) were found to be increased very early after serum induction of Swiss 3T3 fibroblasts and mouse Ehrlich ascites tumour cells, respectively. This rate increase was visible within 10 min, and it was resistant to inhibition by the transcription inhibitor actinomycin D. (2) These two proteins were later shown to be identical to yet another one called 'P21', the mRNA of which was found abundantly in cytoplasmic untranslated mRNP particles in mouse sarcoma ascites cells (Yenofsky et al. 1982). These mRNP particles were considered reserve pools of untranslated mRNAs.

At the beginning of the 1990s, mechanisms of translational control were just being unveiled, and the importance of translation initiation factors in cellular regulation was recognised (reviewed in Clemens and Bommer 1999). In particular, the ability of the cap-binding protein eIF4E to trigger the malignant transformation of cells was discovered at this time (Lazaris-Karatzas et al. 1990). The prevailing hypothesis to explain this crucial role of eIF4E was that certain mRNAs that code for growth-related proteins are highly structured and are therefore poorly translated. Overexpression of eIF4E results in more efficient translation of these mRNAs leading to promotion of cell proliferation. In collaboration with the Sonenberg

lab, we were able to show that the mRNA of TCTP (P23) is one of the mRNAs, the translational efficiency of which is highly dependent on eIF4E (Bommer et al. 1994). Consistent with this, we later demonstrated that TCTP(P23) mRNA is indeed a highly structured molecule (Bommer et al. 2002).

It was only late in the 1990s that the link was established between the PI3K/Akt/mTORC1 growth signalling pathway and the activation of eIF4E via phosphorylation of the inhibitory eIF4E-binding proteins, 4E-BPs (Clemens and Bommer 1999). Also, it became increasingly clear that a subset of mRNAs, i.e. the ones bearing a 5′-terminal oligopyrimidine tract (5′-TOP), is specifically regulated through this pathway. The main representatives of this group of mRNAs are those which encode components of the translational apparatus (Meyuhas and Kahan 2015). Since the TCTP mRNA also features a 5′-TOP (Yamashita et al. 2008), we recently revisited this topic and showed that the growth factor-dependent induction of TCTP synthesis is indeed regulated through the PI3K/Akt/mTORC1 pathway and eIF4E (Bommer et al. 2015). We also found that treatment of colon cancer cells with DNA-damaging anticancer drugs leads to a four-fold up-regulation of TCTP levels through the mTORC1 pathway (Bommer et al. 2017). Similarly, Goodman et al. reported an increase in TCTP levels in muscle hypertrophy and atrophy and its regulation through mTOR signalling (Goodman et al. 2017).

An important negative translational control mechanism operates via phosphorylation of translation initiation factor eIF2α. This phosphorylation event prevents the recycling of the guanosine nucleotide exchange factor for eIF2, eIF2B, and results in the shutdown of protein synthesis. There are four specific protein kinases that are able to phosphorylate eIF2α, each one being activated under very specific cell stress conditions (Clemens and Bommer 1999). One of these, the dsRNA-dependent kinase PKR, is an antiviral enzyme that is activated by double-stranded RNA, which is often formed during viral replication. However, there are also few cellular mRNAs, which are highly structured and able to activate PKR. We have shown that the mRNA for TCTP is one of those mRNA molecules. Due to its structure, it can activate PKR locally and prevent its own translation (Bommer et al. 2002). We have also demonstrated that TCTP mRNA translation is indeed inhibited by PKR in cell stress conditions, as, e.g. in serum starvation (Bommer et al. 2002) or under calcium stress (Bommer et al. 2010).

These findings are consistent with reports on the regulation of other anti-apoptotic proteins, such as Mcl-1, Bcl-XL and survivin. They are all translationally regulated through the mTORC1 pathway [see references in Bommer et al. (2015)], and Mcl-1 is also regulated through PKR (Fritsch et al. 2007).

4.4.2.3 Other Post-transcriptional Regulation

1. *Regulation by Micro-RNAs*. The expression of genes involved in fundamental biological processes, such as development, apoptosis or cancer, are often subject to an additional layer of regulation, by micro-RNAs. This also applies to anti-apoptotic proteins, as they are mentioned above. It is, therefore, appropriate to assume that TCTP would be regulated by micro-RNAs as well. However, reports

on this topic are scarce in the literature; in fact, there are only two papers from 2012 reporting the regulation of TCTP levels by micro-RNAs.

Lo et al. performed a proteomics study on genes differentially expressed in oral cancer patients compared to normal individuals; they found TCTP to be up-regulated in the cancer patient group (Lo et al. 2012). At the same time, the miRNA miR-27b was down-regulated in oral cancer, and expression of miR-27b in two oral cancer cell lines resulted in TCTP levels being reduced to about 30%. In a study to validate an assay for miRNA target identification, Gäken and colleagues used miR-130a as an example. They reported TCTP as the one of the five target mRNAs newly identified by this method, which is regulated to the highest extent (Gaken et al. 2012).

We ourselves attempted to identify micro-RNAs that may target TCTP mRNA. *In-silico* searches revealed several potential target sites in the 3′-UTR of this mRNA; however, our attempts to validate some of these in luciferase reporter gene and in cellular assays did not yield consistent results (UA Bommer, J Clancy and T. Preiss, unpublished observations), and we did not pursue this project further. Thus, the only two reported cases of miRNAs targeting TCTP mRNA are miR-27b and miR-130a.

2. *Regulation of mRNA stability*. In their study on the regulation of TCTP expression by heavy metals, Schmidt et al. found that cobalt and nickel moderately increase TCTP expression through stabilisation of its mRNA (Schmidt et al. 2007). They speculated about the potential role of AUUUA motifs in the 3′-UTR of TCTP mRNA in this process. However, these AUUUA elements do not completely match the 'classical' AU-rich elements (AREs), which in cytokine mRNAs serve to target these RNAs for regulated degradation. The role of these motifs in TCTP mRNA, if any, is yet to be elucidated. Overall, TCTP mRNA was found to be generally fairly stable and abundant in mammalian cells (Yenofsky et al. 1983), although the abundance varies depending on the tissue type (Thiele et al. 2000). Our finding that TCTP mRNA has a high degree of structure (Bommer et al. 2002) is also consistent with the notion that it is a fairly stable RNA molecule.
3. *Protein stability regulation*. There are a few reports, which indicate that in specific instances TCTP protein may be subject to regulated degradation. Two studies described the ability of another anti-apoptotic protein, Mcl-1 (Zhang et al. 2002), and heat-shock protein Hsp27 (Baylot et al. 2012) to stabilise the TCTP protein, which implies that it may be destabilised if those proteins are absent. Kubiak et al. reported that TCTP, a protein involved in maintaining the integrity of the mitotic spindle, is partially degraded during mitotic exit (Kubiak et al. 2008). A novel mechanism for regulated degradation of TCTP protein was published in a very recent paper (see 'Note Added in Proof').

In summary, TCTP levels can be regulated at all levels of gene expression, inclusive of protein stability, although transcriptional and translational regulation of protein expression seems to be the most commonly reported regulatory mechanisms.

4.5 Synopsis

During the 35 years since its original discovery, the translationally controlled tumour protein TCTP has attracted an ever-increasing level of attention. Through a body of well over 300 publications as of today, a considerable number of functional associations of this protein have been established.

Although TCTP is largely a cellular protein, it has also extracellular functions, and its importance in fundamental biological processes often has implications for homeostasis at the whole-organism level. In trying to summarise the functional importance of this protein, the following key words come to mind: cell growth and proliferation, early development, cyto-protection and defence. Many examples studied by today confirm that TCTP is involved in the biological defence against a wide range of cell stresses, in nearly all eukaryotic kingdoms. The specifics of the defence reactions, in which TCTP is engaged, may be quite varied between lower and higher organisms or between plants and animals. What we need now is a deeper understanding of the mechanisms, by which TCTP exerts all these effects.

Naturally, the involvement in these important processes requires a high degree of regulation of both levels and activity of the protein. We do understand some of the underlying mechanisms, but by far not yet all details. Such understanding is of particular importance, since the frequent participation of TCTP in disease processes, such as in cancer, is often due to deregulation of TCTP or due to the exertion of its effects at the wrong time in the wrong place. Promising initial discoveries have been made, identifying TCTP as a potential target in anticancer (or other disease) strategies. We have to learn more about some of the functional interactions of this protein, as well as its regulation, in order eventually to be able to translate this knowledge into meaningful clinical application.

Note Added in Proof

Since the original completion of this manuscript (December 2016) more than half a year has passed, and quite a few new papers on the TCTP protein were published in the meantime. Of these, I just wish to mention the following five publications, which added some interesting new aspects to our understanding of the biology of this protein. (My apology to those colleagues, whose work was not considered here, or even in the main manuscript!)

1. As pointed out in Sect. 4.2.1, there are a large number of publications reporting TCTP as a cyto-protective protein, able to protect cells against a wide range of cytotoxic stresses, inclusive of Ca^{2+}-stress. However, so far, an involvement of TCTP in modulating **ER-stress** and the unfolded protein response (UPR) was not yet described. A recent paper by Pinkaew et al. fills this gap (Pinkaew et al. 2017), by reporting that TCTP (fortilin) binds to the cytoplasmic domain of the ER-stress sensor IRE1α, inhibiting its endonuclease (RNase) and protein kinase activities, and in this way protecting cells against apoptotic cell death.
2. The involvement of TCTP in the cellular process of **autophagy** was studied in a recent paper by the group of Kyunglim Lee (Bae et al. 2017). They found that TCTP interferes with this process in both the mTORC1/AMPK-dependent and

the mTORC1-independent pathway. Thus, TCTP inhibits macroautophagy both at early stages and later at the step of autophagosome maturation. This conclusion contrasts that of another paper (Chen et al. 2014a), cited in Sect. 4.2.3. A possible explanation for this discrepancy is given in the discussion of the more recent paper (Bae et al. 2017).

3. In the very last section of the main text, I mentioned that relatively little is known about the mechanisms involved in **regulation of TCTP degradation**. This gap was closed by a very recent paper by Bonhoure et al. (2017), who showed that TCTP protein can be degraded through the chaperone-mediated autophagy (CMA) pathway. This pathway is different from the process of macroautophagy mentioned in the preceding paragraph. CMA involves the targeting of individual cytoplasmic proteins for lysosomal degradation. In the case of TCTP, it involves the acetylation of the protein at Lysine 19 and its binding to Hsc70, and it requires the activity of lysosome-associated membrane protein type 2A (LAMP-2A). The authors show that this is an underlying mechanism for the down-regulation of TCTP levels under serum-starvation conditions (Bonhoure et al. 2017), which is likely to be corroborated by a block in TCTP mRNA translation (Bommer et al. 2002, 2015).
4. Previous studies on the **role of TCTP in plants**, other than in stress reactions, showed that plant TCTP is important for cell division, growth and development (Sect. 4.2.3). A new study extended these investigations. De Carvalho and colleagues expressed tomato TCTP in tobacco plants and, by transcriptomics analysis, studied the pathways that are differentially regulated as a result of TCTP overexpression (de Carvalho et al. 2017). They observed that genes involved in photosynthesis, fatty acid metabolism and water transport are up-regulated, while genes involved in the synthesis of the phytohormone ethylene were down-regulated. TCTP overexpression also promoted biomass production and it protected plants against salt and osmotic stress. These observations are also consistent with an earlier study that demonstrated the ability of *Arabidopsis thaliana* TCTP to protect tobacco leafs against induction of programmed cell death (Hoepflinger et al. 2013).

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